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(54) **ANTI-EGFR ANTIBODIES AND USES THEREOF**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides antibodies that bind to EGFR and methods of using same. According to certain embodiments of the invention, the antibodies are fully human antibodies that bind to human EGFR with high affinity. In certain embodiments, the antibodies of the present invention are capable of inhibiting the growth of tumor cells expressing high levels of EGFR and/or inducing antibody-dependent cell-mediated cytotoxicity (ADCC) of such cells. The antibodies of the invention are useful for the treatment of various cancers as well as other EGFR-related disorders.

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ANTI-EGFR ANTIBODIES AND USES
THEREOFCROSS-REFERENCE TO RELATED
APPLICATIONS

This application claims the benefit under 35 U.S.C. §119 (e) of US provisional application Nos. 61/663,984, filed on Jun. 25, 2012; and 61/821,000, filed on May 8, 2013, the disclosures of which are herein incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to antibodies, and antigen-binding fragments thereof, which are specific for human EGFR, and methods of use thereof.

BACKGROUND

Epidermal growth factor receptor (EGFR, also known as HER1 or ErbB1) is a member of the ErbB/HER family of type 1 receptor tyrosine kinases (RTKs). Other members of this family include ErbB2 (HER2 or Neu), ErbB3 (HER3) and ErbB4 (HER4). Known ligands for EGFR include epidermal growth factor (EGF) and transforming growth factor alpha (TGF- α). Ligand binding to EGFR induces tyrosine phosphorylation and receptor dimerization with other ErbB family members.

RTKs such as EGFR function to allow cells to respond to diverse external stimuli. However, aberrant activation and/or overexpression of EGFR is associated with the development and progression of several human cancers. Accordingly, EGFR is a target for anti-cancer therapies. Approved drugs targeting EGFR include small molecule inhibitors such as gefitinib (Iressa®) and erlotinib (Tarceva®), and anti-EGFR antibodies such as cetuximab (Erbitux®) and panitumumab (Vectibix®). Anti-EGFR antibodies are mentioned in, e.g., U.S. Pat. No. 4,943,533, U.S. Pat. No. 5,844,093, U.S. Pat. No. 7,060,808, U.S. Pat. No. 7,247,301, U.S. Pat. No. 7,595, 378, U.S. Pat. No. 7,723,484, and U.S. Pat. No. 7,939,072. Nonetheless, there is a need in the art for novel EGFR antagonists, such as anti-EGFR antibodies, for the treatment of cancer and other related disorders.

BRIEF SUMMARY OF THE INVENTION

The present invention provides antibodies that bind human EGFR. The antibodies of the invention are useful, inter alia, for inhibiting EGFR-mediated signaling and for treating diseases and disorders caused by or related to EGFR activity and/or signaling. The antibodies of the invention are also useful for inducing cell death in cells that express high levels of EGFR on their surfaces.

The antibodies of the invention can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, F(ab')₂ or scFv fragment), and may be modified to affect functionality, e.g., to eliminate residual effector functions (Reddy et al., 2000, J. Immunol. 164:1925-1933).

The present invention provides antibodies, or antigen-binding fragments thereof comprising a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, and 370, or a substantially similar

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sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

The present invention also provides an antibody or antigen-binding fragment of an antibody comprising a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, and 378, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

The present invention also provides an antibody or antigen-binding fragment thereof comprising a HCVR and LCVR (HCVR/LCVR) sequence pair selected from the group consisting of SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, and 370/378.

The present invention also provides an antibody or antigen-binding fragment of an antibody comprising a heavy chain CDR3 (HCDR3) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, and 376, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR3 (LCDR3) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, and 384, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

In certain embodiments, the antibody or antigen-binding portion of an antibody comprises a HCDR3/LCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NO: 8/16, 24/32, 40/48, 56/64, 72/80, 88/96, 104/112, 120/128, 136/144, 152/160, 168/176, 184/192, 200/208, 216/224, 232/240, 248/256, 264/272, 280/288, 296/304, 312/320, 328/336, 344/352, 360/368, and 376/384.

The present invention also provides an antibody or fragment thereof further comprising a heavy chain CDR1 (HCDR1) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, and 372, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a heavy chain CDR2 (HCDR2) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, and 374, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a light chain CDR1 (LCDR1) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, and 380, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR2 (LCDR2) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, and 382, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

Certain non-limiting, exemplary antibodies and antigen-binding fragments of the invention comprise HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 domains,

respectively, having the amino acid sequences selected from the group consisting of: SEQ ID NOS: 4-6-8-12-14-16 (e.g. H1M085N); 20-22-24-28-30-32 (e.g. H1M086N); 36-38-40-44-46-48 (e.g. H1M089N); 52-54-56-60-62-64 (e.g. H1M102N); 68-70-72-76-78-80 (e.g. H1M103N); 84-86-88-92-94-96 (e.g. H1M116N); 100-102-104-108-110-112 (e.g. H1H134P); 116-118-120-124-126-128 (e.g. H1H136P); 132-134-136-140-142-144 (e.g. H1H141P); 148-150-152-156-158-160 (e.g., H1H142P); 164-166-168-172-174-176 (e.g. H1H143P); 180-182-184-188-190-192 (e.g., H1H144P); 196-198-200-204-206-208 (e.g. H1H145P); 212-214-216-220-222-224 (e.g. H1H147P); 228-230-232-236-238-240 (e.g. H1H151P); 244-246-248-252-254-256 (e.g. H1H153P); 260-262-264-268-270-272 (e.g. H1H155P); 276-278-280-284-286-288 (e.g. H1H157P); 292-294-296-300-302-304 (e.g. H1H158P); 308-310-312-316-318-320 (e.g. H1H159P); 324-326-328-332-334-336 (e.g. H1H161P); 340-342-344-348-350-352 (e.g. H1H163P); 356-358-360-364-366-368 (e.g. H1H169P); and 372-374-376-380-382-384 (e.g. H1H171P).

In a related embodiment, the invention includes an antibody or antigen-binding fragment of an antibody which specifically binds EGFR, wherein the antibody or fragment comprises the heavy and light chain CDR domains contained within heavy and light chain variable region (HCVR/LCVR) sequences selected from the group consisting of SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, and 370/378. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, e.g., the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. See, e.g., Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani et al., *J. Mol. Biol.* 273: 927-948 (1997); and Martin et al., *Proc. Natl. Acad. Sci. USA* 86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

In another aspect, the invention provides nucleic acid molecules encoding anti-EGFR antibodies or antigen-binding fragments thereof. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

In one embodiment, the invention provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, and 369, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

The present invention also provides an antibody or fragment thereof comprising a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, 345, 361, and 377, or a

substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

The present invention also provides an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 7, 23, 39, 55, 71, 87, 103, 119, 135, 151, 167, 183, 199, 215, 231, 247, 263, 279, 295, 311, 327, 343, 359, and 375, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 31, 47, 63, 79, 95, 111, 127, 143, 159, 175, 191, 207, 223, 239, 255, 271, 287, 303, 319, 335, 351, 367, and 383, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

The present invention also provides an antibody or fragment thereof which further comprises a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195, 211, 227, 243, 259, 275, 291, 307, 323, 339, 355, and 371, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a HCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 5, 21, 37, 53, 69, 85, 101, 117, 133, 149, 165, 181, 197, 213, 229, 245, 261, 277, 293, 309, 325, 341, 357, and 373, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a LCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 11, 27, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, and 379, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 13, 29, 45, 61, 77, 93, 109, 125, 141, 157, 173, 189, 205, 221, 237, 253, 269, 285, 301, 317, 333, 349, 365, and 381, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

According to certain embodiments, the antibody or fragment thereof comprises the heavy and light chain CDR sequences encoded by the nucleic acid sequences of SEQ ID NOS: 1 and 9 (e.g. H1M085N), 17 and 25 (e.g. H1M086N), 33 and 41 (e.g. H1M089N), 49 and 57 (e.g. H1M102N), 65 and 73 (e.g. H1M103N), 81 and 89 (e.g. H1M116N), 97 and 105 (e.g. H1H134P), 113 and 121 (e.g. H1H136P), 129 and 137 (e.g. H1H141P), 145 and 153 (e.g. H1H142P), 161 and 169 (e.g. H1H143P), 177 and 185 (e.g. H1H144P), 193 and 201 (e.g. H1H145P), 209 and 217 (e.g. H1H147P), 225 and 233 (e.g. H1H151P), 241 and 249 (e.g. H1H153P), 257 and 265 (e.g. H1H155P), 273 and 281 (e.g. H1H157P), 289 and 297 (e.g. H1H158P), 305 and 313 (e.g. H1H159P), 321 and 329 (e.g. H1H161P), 337 and 345 (e.g. H1H163P), 353 and 361 (e.g. H1H169P), or 369 and 377 (e.g. H1H171P).

The present invention includes anti-EGFR antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) *JBC* 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

In another aspect, the invention provides a pharmaceutical composition comprising a recombinant human antibody or

fragment thereof which specifically binds EGFR and a pharmaceutically acceptable carrier. In a related aspect, the invention features a composition which is a combination of an anti-EGFR antibody and a second therapeutic agent. In one embodiment, the second therapeutic agent is any agent that is advantageously combined with an anti-EGFR antibody. Exemplary agents that may be advantageously combined with an anti-EGFR antibody include, without limitation, other agents that inhibit EGFR activity (including other antibodies or antigen-binding fragments thereof, peptide inhibitors, small molecule antagonists, etc) and/or agents which do not directly bind EGFR but nonetheless interfere with, block or attenuate EGFR-mediated signaling.

In yet another aspect, the invention provides methods for inhibiting EGFR activity using an anti-EGFR antibody or antigen-binding portion of an antibody of the invention, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody of the invention. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by removal, inhibition or reduction of EGFR activity. The anti-EGFR antibodies or antibody fragments of the invention may function to block the interaction between EGFR and an EGFR binding partner (e.g., epidermal growth factor [EGF], transforming growth factor-alpha [TGF- α], etc.), or otherwise inhibit the signaling activity of EGFR.

The present invention also includes the use of an anti-EGFR antibody or antigen binding portion of an antibody of the invention in the manufacture of a medicament for the treatment of a disease or disorder related to or caused by EGFR activity in a patient.

Other embodiments will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.).

Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All patents, applications and non-patent publications mentioned in this specification are incorporated herein by reference in their entireties.

DEFINITIONS

The expressions "EGFR" and "EGFR fragment," as used herein refer to the human EGFR protein or fragment unless specified as being from a non-human species (e.g., "mouse EGFR," "mouse EGFR fragment," "monkey EGFR," "mon-

key EGFR fragment," etc.). The extracellular domain of human EGFR has the amino acid sequence shown in, e.g., amino acids 25 to 645 of SEQ ID NO:385.

As used herein, "an antibody that binds EGFR" or an "anti-EGFR antibody" includes antibodies, and antigen-binding fragments thereof, that bind a soluble fragment of an EGFR protein (e.g., a portion of the extracellular domain of EGFR) and/or cell surface-expressed EGFR. The expression "cell surface-expressed EGFR" means an EGFR protein or portion thereof that is/are expressed on the surface of a cell in vitro or in vivo, such that at least a portion of the EGFR protein (e.g., amino acids 25 to 645 of SEQ ID NO:385) is exposed to the extracellular side of the cell membrane and accessible to an antigen-binding portion of an antibody. Soluble EGFR molecules include, e.g., monomeric and dimeric EGFR constructs as described in Example 3 herein (i.e., "EGFR.mmh", SEQ ID NO:386, and "EGFR.mFc", SEQ ID NO:387, respectively), or constructs substantially similar thereto.

The term "antibody", as used herein, means any antigen-binding molecule or molecular complex comprising at least one complementarity determining region (CDR) that specifically binds to or interacts with a particular antigen (e.g., EGFR). The term "antibody" includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (e.g., IgM). Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_{H1} , C_{H2} and C_{H3} . Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_L). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In different embodiments of the invention, the FRs of the anti-EGFR antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

The term "antibody", as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g. monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression “antigen-binding fragment,” as used herein.

An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain $V_H-V_H-V_H-V_L$ or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H-C_H1 ; (ii) V_H-C_H2 ; (iii) V_H-C_H3 ; (iv) $V_H-C_H1-C_H2$; (v) $V_H-C_H1-C_H2-C_H3$, (vi) $V_H-C_H2-C_H3$; (vii) V_H-C_L ; (viii) V_L-C_H1 ; (ix) V_L-C_H2 , (x) V_L-C_H3 ; (xi) $V_L-C_H1-C_H2$; (xii) $V_L-C_H1-C_H2-C_H3$; (xiii) $V_L-C_H2-C_H3$; and (xiv) V_L-C_L . In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (e.g., by disulfide bond(s)).

As with full antibody molecules, antigen-binding fragments may be monospecific or multispecific (e.g., bispecific). A multispecific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format, including the exemplary bispecific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

The antibodies of the present invention may function through complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC). “Complement-dependent cytotoxicity” (CDC) refers to lysis of antigen-expressing cells by an antibody of the invention in

the presence of complement. “Antibody-dependent cell-mediated cytotoxicity” (ADCC) refers to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs) (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and thereby lead to lysis of the target cell. CDC and ADCC can be measured using assays that are well known and available in the art. (See, e.g., U.S. Pat. Nos. 5,500,362 and 5,821,337, and Clynes et al. (1998) Proc. Natl. Acad. Sci. (USA) 95:652-656). The constant region of an antibody is important in the ability of an antibody to fix complement and mediate cell-dependent cytotoxicity. Thus, the isotype of an antibody may be selected on the basis of whether it is desirable for the antibody to mediate cytotoxicity.

The term “human antibody”, as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. However, the term “human antibody”, as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The term “recombinant human antibody”, as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire in vivo.

Human antibodies can exist in two forms that are associated with hinge heterogeneity. In one form, an immunoglobulin molecule comprises a stable four chain construct of approximately 150-160 kDa in which the dimers are held together by an interchain heavy chain disulfide bond. In a second form, the dimers are not linked via inter-chain disulfide bonds and a molecule of about 75-80 kDa is formed composed of a covalently coupled light and heavy chain (half-antibody). These forms have been extremely difficult to separate, even after affinity purification.

The frequency of appearance of the second form in various intact IgG isotypes is due to, but not limited to, structural differences associated with the hinge region isotype of the antibody. A single amino acid substitution in the hinge region of the human IgG4 hinge can significantly reduce the appearance of the second form (Angal et al. (1993) Molecular Immunology 30:105) to levels typically observed using a

human IgG1 hinge. The instant invention encompasses antibodies having one or more mutations in the hinge, C_H2 or C_H3 region which may be desirable, for example, in production, to improve the yield of the desired antibody form.

An “isolated antibody,” as used herein, means an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an “isolated antibody” for purposes of the present invention. An isolated antibody also includes an antibody *in situ* within a recombinant cell. Isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

A “neutralizing” or “blocking” antibody, as used herein, is intended to refer to an antibody whose binding to EGFR: (i) interferes with the interaction between EGFR or an EGFR fragment and an EGFR ligand (e.g., EGF, TGF- α , etc.), and/or (ii) results in inhibition of at least one biological function of EGFR. The inhibition caused by an EGFR neutralizing or blocking antibody need not be complete so long as it is detectable using an appropriate assay. Exemplary assays for detecting EGFR inhibition are described herein.

The anti-EGFR antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences from which the antibodies were derived. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as “germline mutations”). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (i.e., a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies of the present invention may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the

original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

The present invention also includes anti-EGFR antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes anti-EGFR antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

The term “epitope” refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

The term “substantial identity” or “substantially identical,” when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95%, and more preferably at least about 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

As applied to polypeptides, the term “substantial similarity” or “substantially similar” means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. A “conservative amino acid substitution” is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, e.g., Pearson (1994) Methods Mol. Biol. 24: 307-331, herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine,

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leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate, and (7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al. (1992) *Science* 256: 1443-1445, herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as Gap and Bestfit which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA using default or recommended parameters, a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. See, e.g., Altschul et al. (1990) *J. Mol. Biol.* 215:403-410 and Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-402, each herein incorporated by reference.

Biological Characteristics of the Antibodies

The present invention includes anti-EGFR antibodies and antigen-binding fragments thereof that bind monomeric or dimeric EGFR molecules with high affinity. For example, the present invention includes antibodies and antigen-binding fragments of antibodies that bind dimeric EGFR with a K_D of less than about 20 pM as measured by surface plasmon resonance, e.g., using the assay format as defined in Example 3 herein. In certain embodiments, the antibodies or antigen-binding fragments of the present invention bind dimeric EGFR with a K_D of less than about 15 pM, less than about 10 pM, less than about 8 pM, less than about 6 pM, less than about 4 pM, less than about 2 pM, or less than about 1 pM, as measured by surface plasmon resonance, e.g., using the assay format as defined in Example 3 herein. The present invention also includes anti-EGFR antibodies and antigen-binding fragments thereof that bind dimeric EGFR with a $t_{1/2}$ of greater than about 200 minutes as measured by surface plasmon resonance, e.g., using the assay format as defined in Example 3 herein. In certain embodiments, the antibodies or antigen-binding fragments of the present invention bind dimeric EGFR with a $t_{1/2}$ of greater than about 210 minutes, greater than about 220 minutes, greater than about 250 minutes, greater than about 260 minutes, greater than about 280 minutes, greater than about 300 minutes, greater than about 320 minutes, greater than about 340 minutes, greater than

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about 360 minutes, greater than about 380 minutes, greater than about 400 minutes, greater than about 450 minutes, greater than about 500 minutes, greater than about 550 minutes, greater than about 600 minutes, greater than about 650 minutes, greater than about 800 minutes, greater than about 1000 minutes, or more, as measured by surface plasmon resonance, e.g., using the assay format as defined in Example 3 herein.

The present invention also includes anti-EGFR antibodies and antigen-binding fragments thereof that inhibit the growth of EGFR-expressing tumor cells. For example, the present invention includes anti-EGFR antibodies and antigen-binding fragments thereof that inhibit the growth of tumor cells that express high levels of EGFR on their surface (e.g., A431 epidermoid carcinoma cells), with an IC_{50} (i.e., the concentration resulting in 50% maximal growth inhibition) of less than about 200 pM. IC_{50} values can be determined using the cell growth inhibition assay exemplified in Example 4 herein, or a substantially similar assay. According to certain embodiments of the present invention the anti-EGFR antibodies or antigen-binding fragments thereof are able to inhibit the growth of A431 cells *in vitro* with an IC_{50} of less than about 180 pM, less than about 160 pM, less than about 140 pM, less than about 120 pM, less than about 100 pM, less than about 80 pM, less than about 60 pM, less than about 40 pM, less than about 20 pM, less than about 10 pM, less than about 5 pM, or less than about 2 pM, as determined using the cell growth inhibition assay exemplified in Example 4 herein, or a substantially similar assay.

The present invention also includes anti-EGFR antibodies and antigen-binding fragments thereof that induce antibody-dependent cell-mediated cytotoxicity (ADCC) of cells that express EGFR. Assays for measuring ADCC are known in the art. An exemplary assay format is illustrated in Example 5 herein, in which anti-EGFR antibodies are added to a cellular mixture of peripheral blood mononuclear cells (PBMCs) and A431 epidermoid carcinoma cells (i.e., cells expressing high levels of EGFR). The extent of cell killing is assessed relative to the maximal cell lysis signal observed under conditions in which untreated cells were lysed by addition of digitonin; the extent of ADCC can thereby be expressed in terms of the percent of maximum cell killing. The present invention includes anti-EGFR antibodies that produce a maximum cell killing percentage of greater than about 25%, when tested in the ADCC assay format of Example 5, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present invention induce ADCC with a maximum cell killing percentage of about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or more, as measured in the ADCC assay format of Example 5 or a substantially similar assay.

The present invention also includes anti-EGFR antibodies and antigen-binding fragments thereof that inhibit tumor growth *in vitro* or *in vivo*. In certain circumstances, the antibodies or antigen-binding fragments of the present invention cause tumor regression or shrinkage. The present invention includes anti-EGFR antibodies and antigen-binding fragments thereof that inhibit the growth of human tumor xenografts in immunocompromised mice. For example, as illustrated in Example 6 herein, the exemplary anti-EGFR antibody H1H141P significantly inhibited the growth of head and neck squamous cell carcinoma cells (e.g., FaDu tumor cells), pancreatic tumor cells (BxPC3), and lung tumor cells (Calu3 and NCI-H358), in mouse xenografts models. The invention includes antibodies and antigen-binding fragments thereof that inhibit tumor cell growth in tumor-bearing mice

by greater than about 50% (e.g., about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or more) as compared to hFc-control-treated tumor-bearing mice.

The present invention also includes anti-EGFR antibodies and antigen binding fragments thereof that induce internalization of cell surface expressed EGFR.

Epitope Mapping and Related Technologies

The present invention includes anti-EGFR antibodies which interact with one or more amino acids found within the extracellular domain of human EGFR (e.g., within extracellular domain I, II, III, and/or IV). The epitope to which the antibodies bind may consist of a single contiguous sequence of 3 or more (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids located within the extracellular domain of EGFR. Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences) located within the extracellular domain of EGFR.

Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody “interacts with one or more amino acids” within a polypeptide or protein. Exemplary techniques include, e.g., routine cross-blocking assay such as that described *Antibodies*, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., N.Y.), alanine scanning mutational analysis, peptide blots analysis (Reineke, 2004, Methods Mol Biol 248:443-463), and peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer, 2000, Protein Science 9:487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water to allow hydrogen-deuterium exchange to occur at all residues except for the residues protected by the antibody (which remain deuterium-labeled). After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antibody interacts. See, e.g., Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem.* 73:256A-265A.

The present invention further includes anti-EGFR antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein (e.g. H1M085N, H1M086N, H1M089N, H1M102N, H1M103N, H1M116N, H1H134P, H1H136P, H1H141P, H1H142P, H1H143P, H1H144P, H1H145P, H1H147P, H1H151P, H1H153P, H1H155P, H1H157P, H1H158P, H1H159P, H1H161P, H1H163P, H1H169P, H1H171P etc.). Likewise, the present invention also includes anti-EGFR antibodies that compete for binding to EGFR with any of the specific exemplary antibodies described herein (e.g. H1M085N, H1M086N, H1M089N, H1M102N, H1M103N, H1M116N, H1H134P, H1H136P, H1H141P, H1H142P, H1H143P, H1H144P, H1H145P, H1H147P, H1H151P, H1H153P, H1H155P, H1H157P, H1H158P, H1H159P, H1H161P, H1H163P, H1H169P, H1H171P etc.).

One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-EGFR antibody by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope as a reference anti-EGFR antibody of the inven-

tion, the reference antibody is allowed to bind to an EGFR protein (e.g., a soluble portion of the EGFR extracellular domain or cell surface-expressed EGFR). Next, the ability of a test antibody to bind to the EGFR molecule is assessed. If 5 the test antibody is able to bind to EGFR following saturation binding with the reference anti-EGFR antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-EGFR antibody. On the other hand, if the test antibody is not able to bind to the EGFR molecule 10 following saturation binding with the reference anti-EGFR antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-EGFR antibody of the invention. Additional routine experimentation (e.g., peptide mutation and binding analyses) can then be carried out to 15 confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, Biacore, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art. In accordance with certain embodiments of the present invention, two antibodies bind to the same (or overlapping) epitope if, e.g., a 1-, 25 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 1990;50:1495-1502). Alternatively, two antibodies are deemed to bind to the same 30 epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies are deemed to have “overlapping epitopes” if only a subset of the amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

To determine if an antibody competes for binding with a reference anti-EGFR antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to an EGFR protein (e.g., a soluble portion of the EGFR extracellular domain or cell surface-expressed EGFR) under saturating conditions followed by assessment of binding of the test antibody to the EGFR molecule. In a second orientation, the test antibody is allowed to bind to an EGFR molecule under saturating conditions followed by assessment of binding of the reference antibody to the EGFR molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the EGFR molecule, then it is concluded that the test antibody and the reference antibody compete for binding to EGFR. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the same epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

Preparation of Human Antibodies

Methods for generating monoclonal antibodies, including fully human monoclonal antibodies are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to human EGFR.

Using VELOCIMMUNE™ technology or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to EGFR are initially isolated having a human variable region and a mouse constant region. 65 As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions

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are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Bioequivalents

The anti-EGFR antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described antibodies but that retain the ability to bind human EGFR. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the anti-EGFR antibody-encoding DNA sequences of the present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an anti-EGFR antibody or antibody fragment that is essentially bioequivalent to an anti-EGFR antibody or antibody fragment of the invention. Examples of such variant amino acid and DNA sequences are discussed above.

Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single doses or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

Bioequivalence may be demonstrated by *in vivo* and *in vitro* methods. Bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

Bioequivalent variants of anti-EGFR antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological

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activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include anti-EGFR antibody variants comprising amino acid changes which modify the glycosylation characteristics of the antibodies, e.g., mutations which eliminate or remove glycosylation. Species Selectivity and Species Cross-Reactivity

According to certain embodiments of the invention, the anti-EGFR antibodies bind to human EGFR but not to EGFR from other species. The present invention also includes anti-EGFR antibodies that bind to human EGFR and to EGFR from one or more non-human species. For example, the anti-EGFR antibodies of the invention may bind to human EGFR and may bind or not bind, as the case may be, to one or more of mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomolgous, marmoset, rhesus or chimpanzee EGFR.

Immunoconjugates

The invention encompasses anti-EGFR monoclonal antibodies conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope. Cytotoxic agents include any agent that is detrimental to cells. Examples of suitable cytotoxic agents and chemotherapeutic agents for forming immunoconjugates are known in the art, (see for example, WO 05/103081).

Multispecific Antibodies

The antibodies of the present invention may be monospecific, bi-specific, or multispecific. Multispecific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al., 1991, J. Immunol. 147:60-69; Kufer et al., 2004, Trends Biotechnol. 22:238-244. The anti-EGFR antibodies of the present invention can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bi-specific or a multispecific antibody with a second binding specificity. For example, the present invention includes bi-specific antibodies wherein one arm of an immunoglobulin is specific for human EGFR or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target or is conjugated to a therapeutic moiety.

An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N,

V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

Therapeutic Formulation and Administration

The invention provides pharmaceutical compositions comprising the anti-EGFR antibodies or antigen-binding fragments thereof of the present invention. The pharmaceutical compositions of the invention are formulated with suitable carriers, excipients, and other agents that provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTINTTM, Life Technologies, Carlsbad, Calif.), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

The dose of antibody administered to a patient may vary depending upon the age and the size of the patient, target disease, conditions, route of administration, and the like. The preferred dose is typically calculated according to body weight or body surface area. When an antibody of the present invention is used for treating a condition or disease associated with EGFR activity in an adult patient, it may be advantageous to intravenously administer the antibody of the present invention normally at a single dose of about 0.01 to about 20 mg/kg body weight, more preferably about 0.02 to about 7, about 0.03 to about 5, or about 0.05 to about 3 mg/kg body weight. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering anti-EGFR antibodies may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (e.g., Mordenti et al., 1991, *Pharmaceut. Res.* 8:1351).

Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al., 1987, *J. Biol. Chem.* 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replace-

able cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but are not limited to AUTOPENTM (Owen Mumford, Inc., Woodstock, UK), DISETRONICTM pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25TM pen, HUMALOGTM pen, HUMALIN 70/30TM pen (Eli Lilly and Co., Indianapolis, Ind.), NOVOPENTM I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIORTM (Novo Nordisk, Copenhagen, Denmark), BDTM pen (Becton Dickinson, Franklin Lakes, N.J.), OPTIPENTM, OPTIPEN PROTTM, OPTIPEN STARLETTTM, and OPTICLIKTM (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but are not limited to the SOLOSTARTM pen (sanofi-aventis), the FLEXPENTTM (Novo Nordisk), and the KWIK-PENTM (Eli Lilly), the SURECLICKTM Autoinjector (Amgen, Thousand Oaks, Calif.), the PENLETTM (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRATTM Pen (Abbott Labs, Abbott Park Ill.), to name only a few.

In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201). In another embodiment, polymeric materials can be used; see, *Medical Applications of Controlled Release*, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Fla. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, 1984, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, *Science* 249:1527-1533.

The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Therapeutic Uses of the Antibodies

The antibodies of the invention are useful, inter alia, for the treatment, prevention and/or amelioration of any disease or disorder associated with or mediated by EGFR expression or activity, or treatable by blocking the interaction between EGFR and an EGFR ligand (e.g., EGF or TGF- α) or otherwise inhibiting EGFR activity and/or signaling, and/or promoting receptor internalization and/or decreasing cell surface receptor number. For example, the antibodies and antigen-binding fragments of the present invention are useful for the treatment of tumors that express high levels of EGFR. The antibodies and antigen-binding fragments of the present invention may be used to treat, e.g., primary and/or metastatic tumors arising in the brain and meninges, oropharynx, lung and bronchial tree, gastrointestinal tract, male and female reproductive tract, muscle, bone, skin and appendages, connective tissue, spleen, immune system, blood forming cells and bone marrow, liver and urinary tract, and special sensory organs such as the eye. In certain embodiments, the antibodies and antigen-binding fragments of the invention are used to treat one or more of the following cancers: renal cell carcinoma, pancreatic carcinoma, breast cancer, head and neck cancer, prostate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (e.g., gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, small cell lung cancer, non-small cell lung cancer (e.g., EGFR-dependent non-small cell lung cancer), synovial sarcoma, thyroid cancer, or melanoma.

Combination Therapies and Formulations

The present invention includes therapeutic administration regimens which comprise administering an anti-EGFR antibody of the present invention in combination with at least one additional therapeutically active component. Non-limiting examples of such additional therapeutically active components include other EGFR antagonists (e.g., a second anti-EGFR antibody [e.g., cetuximab or panitumumab] or small molecule inhibitor of EGFR [e.g., gefitinib or erlotinib]), an antagonist of another EGFR family member such as Her2/ErbB2, ErbB3 or ErbB4 (e.g., anti-ErbB2, anti-ErbB3 or anti-ErbB4 antibody or small molecule inhibitor of ErbB2, ErbB3 or ErbB4 activity), an antagonist of EGFRvIII (e.g., an antibody that specifically binds EGFRvIII), a cMET antagonist (e.g., an anti-cMET antibody), an IGF1R antagonist (e.g., an anti-IGF1R antibody), a B-raf inhibitor (e.g., vemurafenib, sorafenib, GDC-0879, PLX-4720), a PDGFR- α inhibitor (e.g., an anti-PDGFR- α antibody), a PDGFR- β inhibitor (e.g., an anti-PDGFR- β antibody), a VEGF antagonist (e.g., a VEGF-Trap, see, e.g., U.S. Pat. No. 7,087,411 (also referred to herein as a "VEGF-inhibiting fusion protein"), anti-VEGF antibody (e.g., bevacizumab), a small molecule kinase inhibitor of VEGF receptor (e.g., sunitinib, sorafenib or pazopanib)), a DLL4 antagonist (e.g., an anti-DLL4 antibody disclosed in US 2009/0142354 such as REGN421), an Ang2 antagonist (e.g., an anti-Ang2 antibody disclosed in US 2011/0027286 such as H1H685P), etc. Other agents that may be beneficially administered in combination with the anti-EGFR antibodies of the invention include cytokine inhibitors,

including small-molecule cytokine inhibitors and antibodies that bind to cytokines such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-11, IL-12, IL-13, IL-17, IL-18, or to their respective receptors.

The present invention also includes therapeutic combinations comprising any of the anti-EGFR antibodies mentioned herein and an inhibitor of one or more of VEGF, Ang2, DLL4, ErbB2, ErbB3, ErbB4, EGFRvIII, cMet, IGF1R, B-raf, PDGFR- α , PDGFR- β , or any of the aforementioned cytokines, wherein the inhibitor is an aptamer, an antisense molecule, a ribozyme, an siRNA, a peptibody, a nanobody or an antibody fragment (e.g., Fab fragment; F(ab')₂ fragment; Fd fragment; Fv fragment; scFv; dAb fragment; or other engineered molecules, such as diabodies, triabodies, tetrabodies, minibodies and minimal recognition units). The anti-EGFR antibodies of the invention may also be administered and/or co-formulated in combination with antivirals, antibiotics, analgesics, corticosteroids and/or NSAIDs. The anti-EGFR antibodies of the invention may also be administered as part of a treatment regimen that also includes radiation treatment and/or conventional chemotherapy.

The additional therapeutically active component(s) may be administered just prior to, concurrent with, or shortly after the administration of an anti-EGFR antibody of the present invention; (for purposes of the present disclosure, such administration regimens are considered the administration of an anti-EGFR antibody "in combination with" an additional therapeutically active component). The present invention includes pharmaceutical compositions in which an anti-EGFR antibody of the present invention is co-formulated with one or more of the additional therapeutically active component(s) as described elsewhere herein.

The present invention also includes compositions and methods comprising a combination of a "degrading antibody" and a "ligand-blocking antibody." A "degrading antibody" means an anti-EGFR antibody that causes degradation of EGFR in cells without necessarily blocking ligand-receptor interactions. A non-limiting example of a degrading antibody of the present invention is the antibody designated H1H134P. A "ligand-blocking antibody" means an anti-EGFR antibody that blocks the interaction between EGFR and one or more of its ligands (e.g., EGF or TGF- α). A non-limiting example of a ligand-blocking antibody of the present invention is the antibody designated H1H141P. Another example of a ligand blocking antibody is cetuximab. The present inventors have conceived of combining a degrading antibody and a ligand-blocking antibody in order to synergistically or otherwise improve anti-tumor efficacy. Accordingly, the present invention includes pharmaceutical compositions comprising at least one degrading antibody and at least one ligand-blocking antibody. The present invention also includes therapeutic methods comprising administering to a subject a combination of a degrading antibody and a ligand-blocking antibody (either as separate administrations or as co-formulations).

Diagnostic Uses of the Antibodies

The anti-EGFR antibodies of the present invention may also be used to detect and/or measure EGFR, or EGFR-expressing cells in a sample, e.g., for diagnostic purposes. For example, an anti-EGFR antibody, or fragment thereof, may be used to diagnose a condition or disease characterized by aberrant expression (e.g., over-expression, under-expression, lack of expression, etc.) of EGFR. Exemplary diagnostic assays for EGFR may comprise, e.g., contacting a sample, obtained from a patient, with an anti-EGFR antibody of the invention, wherein the anti-EGFR antibody is labeled with a detectable label or reporter molecule. Alternatively, an unla-

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beled anti-EGFR antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I ; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, beta-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure EGFR in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

Samples that can be used in EGFR diagnostic assays according to the present invention include any tissue or fluid sample obtainable from a patient which contains detectable quantities of EGFR protein, or fragments thereof, under normal or pathological conditions. Generally, levels of EGFR in a particular sample obtained from a healthy patient (e.g., a patient not afflicted with a disease or condition associated with abnormal EGFR levels or activity) will be measured to initially establish a baseline, or standard, level of EGFR. This baseline level of EGFR can then be compared against the levels of EGFR measured in samples obtained from individuals suspected of having a EGFR related disease or condition.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1

Generation of Human Antibodies to EGFR

An EGFR-expressing cell line was administered directly, with an adjuvant to stimulate the immune response, to a

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VELOCIMMUNE® mouse comprising DNA encoding human Immunoglobulin heavy and kappa light chain variable regions. The antibody immune response was monitored by a EGFR-specific immunoassay. When a desired immune response was achieved splenocytes were harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines were screened and selected to identify cell lines that produce EGFR-specific antibodies. Using this technique several anti-EGFR chimeric antibodies (i.e., antibodies possessing human variable domains and mouse constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H1M085N, H1M086N, H1M089N, H1M102N, H1M103N, and H1M116N.

Anti-EGFR antibodies were also isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in US 2007/0280945A1. Using this method, several fully human anti-EGFR antibodies (i.e., antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H1H134P, H1H136P, H1H141P, H1H142P, H1H143P, H1H144P, H1H145P, H1H147P, H1H151P, H1H153P, H1H155P, H1H157P, H1H158P, H1H159P, H1H161P, H1H163P, H1H169P, and H1H171P.

Certain biological properties of the exemplary anti-EGFR antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2

Heavy and Light Chain Variable Region Amino Acid Sequences

Table 1 sets forth the heavy and light chain variable region amino acid sequence pairs of selected anti-EGFR antibodies and their corresponding antibody identifiers.

TABLE 1

Antibody Designation	SEQ ID NOs:							
	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3
085N	2	4	6	8	10	12	14	16
086N	18	20	22	24	26	28	30	32
089N	34	36	38	40	42	44	46	48
102N	50	52	54	56	58	60	62	64
103N	66	68	70	72	74	76	78	80
116N	82	84	86	88	90	92	94	96
134P	98	100	102	104	106	108	110	112
136P	114	116	118	120	122	124	126	128
141P	130	132	134	136	138	140	142	144
142P	146	148	150	152	154	156	158	160
143P	162	164	166	168	170	172	174	176
144P	178	180	182	184	186	188	190	192
145P	194	196	198	200	202	204	206	208
147P	210	212	214	216	218	220	222	224
151P	226	228	230	232	234	236	238	240
153P	242	244	246	248	250	252	254	256
155P	258	260	262	264	266	268	270	272
157P	274	276	278	280	282	284	286	288
158P	290	292	294	296	298	300	302	304
159P	306	308	310	312	314	316	318	320
161P	322	324	326	328	330	332	334	336
163P	338	340	342	344	346	348	350	352
169P	354	356	358	360	362	364	366	368
171P	370	372	374	376	378	380	382	384

Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (e.g. "H1H" or "H1M"), followed by a numerical identifier (e.g. "085" or "134" as shown in Table 1), followed by a "P" or "N" suffix. Thus, according to this nomenclature, an antibody may be referred to herein as, e.g., "H1M085N" or "H1H134P", etc. The H1H and H1M prefixes on the antibody designations used herein indicate the particular Fc region of the antibody. For example, an "H1M" antibody has a mouse IgG1 Fc, whereas an "H1H" antibody has a human IgG1 Fc. As will be appreciated by a person of ordinary skill in the art, an H1M antibody can be converted to an H1H antibody, and vice versa, but in any event, the variable domains (including the CDRs)—which are indicated by the numerical identifiers shown in Table 1—will remain the same.

Control Constructs Used in the Following Examples

Various control constructs (anti-EGFR antibodies) were included in the following experiments for comparative purposes. The control constructs are designated as follows: Control I: a chimeric anti-EGFR antibody with heavy and light chain variable sequences of "mAb 225" as set forth in U.S. Pat. No. 7,060,808; and Control II: a commercially available fully human monoclonal anti-EGFR antibody designated as ABX-EGF, also known as Panitumumab or Vectibix®.

Example 3

Antibody Binding to Human EGFR as Determined by Surface Plasmon Resonance

Equilibrium dissociation constants (K_D values) for antigen binding to selected purified anti-human EGFR monoclonal antibodies were determined using a real-time surface plasmon resonance biosensor (Biacore T100) assay at 37° C. The Biacore sensor surface was derivatized with monoclonal mouse anti-human Fc antibody (GE Biosciences) to capture anti-EGFR monoclonal antibodies, expressed in the human IgG1 Fc format (antibody prefix H1H). Different concentrations of human monomeric (EGFR.mmh; SEQ ID NO:386) and dimeric (EGFR.mFc; SEQ ID NO:387) proteins were injected over the anti-EGFR monoclonal antibody captured surface at a flow rate of 50 μ l/min. Antibody-antigen association was monitored for 4-5 minutes while dissociation of antigen from the captured monoclonal antibody surface was monitored for 10 min. Kinetic association (k_a) and dissociation (k_d) rate constants were determined by processing and fitting the data to a 1:1 binding model using Scrubber 2.0 curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives ($t_{1/2}$) were calculated from the kinetic rate constants as: K_D (M)= k_d/k_a ; and $t_{1/2}$ (min)=($\ln 2/(60 \cdot k_d)$). Kinetic binding parameters for different anti-EGFR monoclonal antibodies are shown in Table 2.

TABLE 2

Binding Characteristics of Anti-EGFR Antibodies to Monomeric and Dimeric EGFR

Antibody	Analyte	k_a (Ms ⁻¹)	k_d (s ⁻¹)	K_D (Molar)	$t_{1/2}$ (min)
H1H0085N	EGFR.mmh	1.19E+05	1.85E-03	1.55E-08	6
	EGFR.mFc	3.36E+05	4.05E-05	1.20E-10	286
H1H086N	EGFR.mmh	5.40E+05	7.08E-04	1.31E-09	16
	EGFR.mFc	1.90E+06	1.13E-05	5.98E-12	1018

TABLE 2-continued

Binding Characteristics of Anti-EGFR Antibodies to Monomeric and Dimeric EGFR					
		k_a (Ms ⁻¹)	k_d (s ⁻¹)	K_D (Molar)	$t_{1/2}$ (min)
5	H1H089N	EGFR.mmh	3.13E+05	6.83E-03	2.18E-08
		EGFR.mFc	1.49E+06	4.49E-05	3.01E-11
10	H1H102N	EGFR.mmh	1.66E+05	9.43E-04	5.67E-09
		EGFR.mFc	8.63E+05	5.62E-05	6.51E-11
15	H1H103N	EGFR.mmh	1.00E+05	1.39E-03	1.39E-08
		EGFR.mFc	3.83E+05	4.19E-05	1.09E-10
20	H1H116N	EGFR.mmh	5.39E+05	2.84E-03	5.27E-09
		EGFR.mFc	1.55E+06	3.16E-05	2.03E-11
25	H1H134P	EGFR.mmh	9.30E+05	7.89E-04	8.48E-10
		EGFR.mFc	3.09E+06	2.47E-05	7.99E-12
30	H1H136P	EGFR.mmh	NB	NB	NB
		EGFR.mFc	NB	NB	NB
35	H1H141P	EGFR.mmh	3.96E+05	4.05E-04	1.02E-09
		EGFR.mFc	9.03E+05	7.51E-06	8.31E-12
40	H1H142P	EGFR.mmh	1.58E+05	6.89E-04	4.35E-09
		EGFR.mFc	3.61E+05	1.20E-05	3.32E-11
45	H1H143P	EGFR.mmh	1.27E+05	7.27E-04	5.71E-09
		EGFR.mFc	3.81E+05	1.35E-05	3.54E-11
50	H1H144P	EGFR.mmh	1.84E+05	9.67E-04	5.25E-09
		EGFR.mFc	8.94E+05	1.94E-05	2.17E-11
55	H1H145P	EGFR.mmh	1.37E+05	1.95E-04	1.43E-09
		EGFR.mFc	2.52E+05	5.86E-05	2.32E-10
60	H1H147P	EGFR.mmh	6.54E+04	3.76E-04	5.76E-09
		EGFR.mFc	1.90E+05	1.26E-05	6.64E-11
65	H1H151P	EGFR.mmh	1.34E+05	1.13E-03	8.40E-09
		EGFR.mFc	1.34E+05	1.13E-03	8.40E-09
70	H1H153P	EGFR.mmh	7.61E+04	2.35E-04	3.09E-09
		EGFR.mFc	2.34E+05	8.23E-06	3.51E-11
75	H1H155P	EGFR.mmh	1.76E+05	1.69E-04	9.62E-10
		EGFR.mFc	3.29E+05	1.06E-04	3.21E-10
80	H1H157P	EGFR.mmh	NB	NB	NB
		EGFR.mFc	NB	NB	NB
85	H1H158P	EGFR.mmh	1.31E+05	7.73E-04	5.90E-09
		EGFR.mFc	4.08E+05	9.84E-06	2.41E-11
90	H1H159P	EGFR.mmh	4.76E+05	3.25E-04	6.82E-10
		EGFR.mFc	1.64E+06	5.63E-06	3.44E-12
95	H1H161P	EGFR.mmh	4.89E+05	3.21E-04	6.55E-10
		EGFR.mFc	1.73E+06	2.76E-06	1.59E-12
100	H1H163P	EGFR.mmh	5.11E+05	4.26E-04	8.34E-10
		EGFR.mFc	1.81E+06	2.12E-06	1.17E-12
105	H1H169P	EGFR.mmh	6.65E+05	8.69E-04	1.31E-09
		EGFR.mFc	2.29E+06	1.69E-05	7.36E-12
110	H1H171P	EGFR.mmh	7.94E+04	1.13E-03	1.42E-08
		EGFR.mFc	3.39E+05	3.48E-05	1.03E-10
115	Control I	EGFR.mmh	1.58E+06	7.38E-03	4.68E-09
		EGFR.mFc	3.55E+06	1.08E-04	3.03E-11
120	Control II	EGFR.mmh	7.12E+05	7.62E-04	1.07E-09
		EGFR.mFc	1.38E+06	5.82E-05	4.23E-11

As shown in Table 2, several of the anti-EGFR antibodies of the present invention exhibited superior binding properties as compared to the control antibodies. For example, certain anti-EGFR antibodies of the present invention exhibited K_D values less than 10 pM and $t_{1/2}$ values greater than 400 minutes, when tested for binding to dimeric EGFR ("EGFR.mFc") in the surface plasmon resonance assay described above; e.g., H1H086N (5.98 pM/1018 min), H1H134P (7.99 pM/468 min), H1H141P (8.31 pM/1539 min), H1H159P (3.44 pM/2059 min), H1H161P (1.59 pM/4187 min), and H1H169P (7.36 pM/684 min). By contrast, Control I exhibited a K_D of 30.3 pM and a $t_{1/2}$ of 107 min, and Control II exhibited a K_D of 42.3 pM and a $t_{1/2}$ of 198 min when tested for binding to dimeric EGFR under identical experimental conditions.

Example 4

Inhibition of Cell Growth by Anti-EGFR Antibodies

Anti-EGFR antibodies were tested for their ability to inhibit the growth of A431 epidermoid carcinoma cells in

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vitro. A431 cells have an amplification of the EGFR gene and exhibit a strong dependence on EGFR signaling for growth. A431 cells were seeded at a density of 5.0×10^3 cells per well in 96-well plates and incubated in DMEM medium containing 0.5% BSA and 1% penicillin/streptomycin/glutamine. EGFR-specific mAbs were added to cells in 1:3 serial dilutions starting at 60 nM. After 7 days viable cells were quantified by staining with Alamar Blue (Invitrogen) and measuring fluorescence with a Flexstation III spectrophotometer. Absorbance values were plotted using a four-parameter logistic equation over the 12-point dilution series (GraphPad Prism). Results are summarized in Table 3.

TABLE 3

Relative Inhibition of A431 Cell Proliferation by Anti-EGFR Antibodies	
Antibody	IC ₅₀ of A431 Proliferation (Molar)
H1H0085N	1.645E-09
H1H086N	5.459E-10
H1H089N	2.305E-09
H1H102N	2.883E-10
H1H103N	3.89E-09
H1H116N	2.24E-10
H1H134P	1.844E-09
H1H136P	No Inhibition
H1H141P	1.405E-10
H1H142P	5.474E-10
H1H143P	9.968E-11
H1H144P	1.393E-11
H1H145P	No Inhibition
H1H147P	9.769E-11
H1H151P	2.77E-10
H1H153P	No Inhibition
H1H155P	No Inhibition
H1H157P	No Inhibition
H1H158P	No Inhibition
H1H159P	No Inhibition
H1H161P	No Inhibition
H1H163P	No Inhibition
H1H169P	No Inhibition
H1H171P	No Inhibition
Control I	3.346E-10

As shown in Table 3, the tested antibodies exhibited a broad range of IC₅₀ values with some antibodies possessing little to no blocking activity while others displayed IC₅₀ values lower than the reference Control I antibody. For example, anti-EGFR antibodies H1H141P, H1H143P, H1H144P and H1H147P all exhibited IC₅₀ values less than 200 pM, whereas, the Control I antibody exhibited an IC₅₀ value of greater than 334 pM.

Example 5

Induction of ADCC on A431 Cells by Anti-EGFR Antibodies

Antibody dependent cell-mediated cytotoxicity (ADCC) is a cellular process which occurs when Fc receptors on natural killer cells are activated to induce the release of cell-lysing enzymes against target cells. The ability of anti-EGFR antibodies to induce ADCC in vitro was assessed by using peripheral blood mononuclear cells (PBMC) as effector, or primary "killer" cells, against A431 target cells that endogenously over-express EGFR.

Briefly, anti-EGFR antibodies over a broad concentration range (40 nM-0 nM; 1:3 dilutions) were added to a cellular mixture of PBMC and A431 cells (30:1 ratio) in 96-well plates. The plates were incubated for 4 hours at 37° C., 5%

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CO₂, equilibrated to room temperature for 10 minutes and CytoTox-Glo reagent was added to the wells. Untreated cells in control wells were lysed by addition of digitonin to determine maximal cell lysis signal. The plates were incubated briefly at room temperature and luminescence was measured from each well using a plate reader.

Cytotoxic response was calculated by subtracting the signal for A431 cells incubated with PBMC without the addition of anti-EGFR antibodies (background) from the signal generated from target cells mixed with PBMC in the presence of anti-EGFR mAbs. The percentage of cytotoxicity was calculated by dividing the cytotoxic response of cells against background by the maximal cytotoxic response obtained from cell lysis via digitonin. Data was analyzed by a four-parameter logistical equation with a sigmoidal dose-response curve (Graph Pad Prism). Results are summarized in Table 4. (NA=no activity).

TABLE 4

ADCC Activity of Selected Anti-EGFR Antibodies		
Antibody	EC ₅₀ (Molar)	Maximum Cell Killing (%)
H1H0085N	3.70E-13	35
H1H086N	2.91E-13	25
H1H089N	5.83E-12	53
H1H102N	4.39E-13	48
H1H103N	7.25E-13	17
H1H116N	2.51E-13	29
H1H134P	4.61E-11	33
H1H136P	1.49E-09	27
H1H141P	2.78E-12	41
H1H142P	1.19E-12	34
H1H143P	NA	13
H1H144P	4.57E-11	43
H1H145P	NA	0
H1H147P	NA	13
H1H151P	5.48E-09	68
H1H153P	2.65E-11	31
H1H155P	1.67E-11	30
H1H157P	2.27E-13	36
H1H158P	2.32E-12	28
H1H159P	2.69E-09	60
H1H161P	9.80E-12	38
H1H163P	2.96E-10	48
H1H169P	4.81E-09	27
H1H171P	8.94E-13	27
Control I	1.86E-12	24

As shown in Table 4, several anti-EGFR mAbs induced ADCC on A431 cells co-incubated with PBMC effector cells. Additionally, several anti-EGFR mAbs demonstrate a high maximal cell killing percentage comparable to the control antibody (Control I). For example, anti-EGFR antibodies H1H089N, H1H102N, H1H141P, H1H144P, H1H151P, H1H159P and H1H163P each exhibited greater than 40% maximum cell killing in the ADCC assay, whereas the Control I antibody exhibited less than 25% maximum cell killing in this assay.

Example 6

Inhibition of Tumor Growth by an Anti-EGFR Antibody

The anti-EGFR antibody H1H141P was tested for its ability to inhibit the growth human tumor xenografts in immunocompromised mice. Briefly, 2x10⁶ FaDu head and neck squamous cell carcinoma cells were implanted subcutaneously into the flank of C.B.-17 SCID mice. After tumors

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reached an average size of approximately 200 mm³ mice were randomized into groups for treatment (N=6 mice per group) and injected twice per week subcutaneously with either human Fc control protein (12.5 mg/kg; SEQ ID NO:388) or with H1H141P (10 mg/kg). Mice were treated for 15 days.

Tumor volumes were measured twice per week throughout the experiment and tumor weights were determined upon excision at the conclusion of the experiment. The average tumor growth (the average change in tumor volume from the start of treatment through the end of the experiment) and the average tumor weights were determined for each group. Results are summarized in Table 5.

TABLE 5

Inhibition of FaDu Tumor Growth in SCID Mice					
Antibody (mg/kg)	Tumor Growth (mm ³)		% De- crease in from start of treatment (mean ± SD)		% De- crease in Tumor Weight vs Control (mean ± SD)
	Tumor Growth vs Control (mean ± SD)	Tumor Weight vs Control (mean ± SD)	Tumor Growth vs Control (mean ± SD)	Tumor Weight vs Control (mean ± SD)	
hFc Control (12.5)	1099 ± 186	—	0.993 ± 0.176	—	
H1H141P (10)	55 ± 115	95	0.215 ± 0.120	78	

In a similar experiment, the effect of H1H141P on the growth of BxPC3 pancreatic tumor xenografts was determined, as summarized in Table 6.

TABLE 6

Inhibition of BxPC3 Tumor Growth in SCID Mice					
Antibody (mg/kg)	Tumor Growth (mm ³)		% De- crease in Tumor Growth vs Control (mean ± SD)		% De- crease in Tumor Weight vs Control (mean ± SD)
	Tumor Growth vs Control (mean ± SD)	Tumor Weight vs Control (mean ± SD)	Tumor Growth vs Control (mean ± SD)	Tumor Weight vs Control (mean ± SD)	
hFc Control (25)	706 ± 277	—	0.926 ± 0.412	—	
H1H141P (12.5)	97 ± 59	86	0.275 ± 0.098	70	

In a similar experiment, the effect of H1H141P on the growth of Calu3 lung tumor xenografts was determined, as summarized in Table 7.

SEQUENCE LISTING

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28

TABLE 7

Antibody (mg/kg)	Inhibition of Calu3 Tumor Growth in SCID Mice		Tumor Weight vs Control (mean ± SD)	% Decrease in Tumor Weight vs Control
	Tumor Growth (mm ³) from start of treatment (mean ± SD)	% De- crease in Tumor Growth vs Control		
hFc Control (25)	656 ± 202	—	0.884 ± 0.275	—
H1H141P (25)	335 ± 58	49	0.582 ± 0.097	34

In a similar experiment, the effect of H1H141P on the growth of NCI-H358 lung tumor xenografts was determined, as summarized in Table 8.

TABLE 8

Antibody (mg/kg)	Inhibition of NCI-H358 Tumor Growth in SCID Mice		% Decrease in Tumor Growth vs Control
	Tumor Growth (mm ³) from start of treatment (mean ± SD)	% De- crease in Tumor Weight vs Control	
hFc Control (25)	329 ± 170	—	—
H1H141P (12.5)	(-14) ± 47	104	

In a similar experiment, the effect of H1H141P on the growth of A431 epidermoid carcinoma xenografts was determined, as summarized in Table 9.

TABLE 9

Antibody (mg/kg)	Inhibition of A431 Tumor Growth in SCID Mice		% Decrease in Tumor Growth vs Control
	Tumor Growth (mm ³) from start of treatment (mean ± SD)	% De- crease in Tumor Weight vs Control	
hFc Control (25)	134 ± 173	—	—
H1H141P (12.5)	62 ± 49	95	
H1H141P (25)	45 ± 60	97	

Collectively, these findings indicate that H1H141P as a monotherapy can inhibit the growth of multiple human tumor xenografts, representing several different tumor types.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

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 35          40           45

Ser Gly Ile Asn Trp Asn Ser Asp Lys Ile Ala Tyr Ala Asp Ser Val
 50          55           60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Ser Leu Phe
 65          70           75           80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
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Gly Thr Leu Val Thr Val Ser Ser
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Pro	His	Leu	Leu	Ile	Tyr	Leu	Val	Ser	Thr	Arg	Ala	Ser	Gly	Val	Pro
50					55				60						

Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65					70				75				80		

Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Ile	Gln	Ala
								85	90				95		

Leu	Gln	Thr	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys
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ggggactctg	tgaaggggccg	attcaccatc	tccagagaca	acggccgagaa	ctcccgttt	240
ctgcaaatga	atagttctgag	acctgaggac	acggcccttgt	attactgtgt	aaaaaggggc	300
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Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Asn Trp Asn Ser Asp Lys Ile Ala Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Ser Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
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tacactgcaga agccaggggca gtctccacac ctctctgtatct atttgggttc tactcgcc 180
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35	40	45	
Pro His Leu Leu Ile Tyr Leu Val Ser Thr Arg Ala Ser Gly Val Pro			
50	55	60	
Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile			
65	70	75	80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala			
85	90	95	
Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys			
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gcccactctg tgaaggggccg attcaccatc tccagagaca acgcccggaaa ctccctgttt	240
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 35 40 45

Ser Gly Ile Asn Trp Asn Ser Asp Lys Ile Ala Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Ser Leu Phe
 65 70 75 80

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Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
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<210> SEQ ID NO 37
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 37

attaatttggaa atagtgataa aata

24

<210> SEQ ID NO 38
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 38

Ile Asn Trp Asn Ser Asp Lys Ile
1 5

<210> SEQ ID NO 39
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 39

gtaaaaaagggg gcgcgttttg gactgattat tatgactat

39

<210> SEQ ID NO 40
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 40

Val	Lys	Arg	Gly	Asp	Phe	Trp	Thr	Asp	Tyr	Tyr	Asp	Tyr
1				5			10					

<210> SEQ ID NO 41

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 41

gatattgtga	tgactcagtc	tccactctcc	ctgcccgtca	ccccctggaga	gccggccctcc	60
atctcctgc	ggtcttagtca	gagcctcctt	catacataatg	gacacaacta	tttggatgg	120
tacctgcaga	agccaggca	gtctccacac	ctcctgatct	atttggtttc	taatcgcc	180
tccggggtcc	ctgacaggtt	cagtggcagt	ggatcaggca	cagatttac	actgaaaatc	240
agcagagtg	aggctgagga	tgttggagtt	tattactgca	tacaggctct	acaaactccg	300
tggacgttcg	gccaaggac	caagggtggaa	atcaaa			336

<210> SEQ ID NO 42

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 42

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
1				5			10				15				

Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser
				20				25				30			

Asn	Gly	His	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
				35			40				45				

Pro	His	Leu	Leu	Ile	Tyr	Leu	Val	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro
				50			55			60					

Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
				65			70		75		80				

Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Ile	Gln	Ala
				85			90				95				

Leu	Gln	Thr	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys
				100			105			110					

<210> SEQ ID NO 43

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 43

cagagcgtcc	ttcatacgtaa	tggacacaac	tat			33
------------	-------------	------------	-----	--	--	----

<210> SEQ ID NO 44

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 44

Gln Ser Leu Leu His Ser Asn Gly His Asn Tyr
 1 5 10

<210> SEQ ID NO 45

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 45

ttggtttct

9

<210> SEQ ID NO 46

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 46

Leu Val Ser

1

<210> SEQ ID NO 47

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 47

atacaggctc tacaaaactcc gtggacg

27

<210> SEQ ID NO 48

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 48

Ile Gln Ala Leu Gln Thr Pro Trp Thr
 1 5

<210> SEQ ID NO 49

<211> LENGTH: 357

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 49

caggtgcagc tgcaggagtc gggcccagga ctgggtgcagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccgtcagc agtgttgact actactggag ctggatccgc 120

cagcacccag ggaaggccct ggagtggatt ggacacatct attacagttt gatcacctac 180

tacaacccgt ccctcgagag tcgagttacc ataacactgg acacgtctaa gaaccaggta 240

tccctgaacc tgagatctgt gactgcccg gacacggccg tgcattactg tgcgagaacg 300

gctataattt gaactatgga caactggggc cggggaaacc cttgtcacccgt ctcctca 357

<210> SEQ ID NO 50

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-continued

<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 50

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Gln	Pro	Ser	Gln
1				5				10					15		

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Val Ser Ser Gly

20				25				30							
----	--	--	--	----	--	--	--	----	--	--	--	--	--	--	--

Asp Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu

35				40				45							
----	--	--	--	----	--	--	--	----	--	--	--	--	--	--	--

Trp Ile Gly His Ile Tyr Tyr Ser Gly Ile Thr Tyr Tyr Asn Pro Ser

50				55				60							
----	--	--	--	----	--	--	--	----	--	--	--	--	--	--	--

Leu Glu Ser Arg Val Thr Ile Thr Leu Asp Thr Ser Lys Asn Gln Phe

65				70				75				80			
----	--	--	--	----	--	--	--	----	--	--	--	----	--	--	--

Ser Leu Asn Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val His Tyr

85				90				95							
----	--	--	--	----	--	--	--	----	--	--	--	--	--	--	--

Cys Ala Arg Thr Ala Ile Ile Gly Thr Met Asp Asn Trp Gly Arg Gly

100				105				110							
-----	--	--	--	-----	--	--	--	-----	--	--	--	--	--	--	--

Thr Leu Val Thr Val Ser Ser

115															
-----	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

<210> SEQ ID NO 51
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 51

ggtggtccg tcagcagtgg tgactactac 30

<210> SEQ ID NO 52
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 52

Gly Gly Ser Val Ser Ser Gly Asp Tyr Tyr

1 5 10

<210> SEQ ID NO 53
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 53

atctattaca gtgggatcac c 21

<210> SEQ ID NO 54
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 54

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Ile Tyr Tyr Ser Gly Ile Thr
1 5

<210> SEQ ID NO 55
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 55

gcgagaacgg ctataattgg aactatggac aac 33

<210> SEQ ID NO 56
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 56

Ala Arg Thr Ala Ile Ile Gly Thr Met Asp Asn
1 5 10

<210> SEQ ID NO 57
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 57

gaaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccaggggaa aagagccact 60
ctctcctgca gggccagtca gagtgtttagc agcaacttag cctggtagcca gcagaaacct 120
ggccaggctc ccaggctcct catctatgtat gcatccacca gggccactgg tttcccagcc 180
aggttcagtg gcagtgggtc tgggacagaa ttcaactctca ccatcagcag cctgcagtc 240
gaagattttg cagtttatta ctgtcagcaa tataatacct ggtggacggtt cggccaagg 300
accaagggtgg aaatcaaa 318

<210> SEQ ID NO 58
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 58

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Arg Ala Thr Gly Phe Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Thr Trp Trp Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

-continued

100 105

<210> SEQ ID NO 59
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 59

cagagtgtta gcagcaac

18

<210> SEQ ID NO 60
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 60

Gln Ser Val Ser Ser Asn
1 5

<210> SEQ ID NO 61
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 61

gatgcattc

9

<210> SEQ ID NO 62
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 62

Asp Ala Ser
1

<210> SEQ ID NO 63
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 63

cagcaatata atacctggtg gacg

24

<210> SEQ ID NO 64
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 64

Gln Gln Tyr Asn Thr Trp Trp Thr
1 5

<210> SEQ ID NO 65

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<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 65

gaggtgcagc tggtgaggc tgggtacagc ctgggggtc cctgagactc      60
tcctgtcgac cctctggatt cacccatcgat agttacgaca tgcactgggt ccgc当地
acaggaaaag gtcttagagt ggtctcaggat attggtaactt ctggagatac atactatcca    180
ggctccgtga aggcccatt caccatctcc agagaagatc ccaagaatc cctgtatctt    240
caaataata gcctgagagc cggggacacg gctgtatatt actgtgcaag agtgggatatt 300
gactggaaact tcgtcgatt tgactactgg ggccaggaa ccctggtcaac cgtctccctca 360

```

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<210> SEQ ID NO 66
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 66

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1           5          10          15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20          25          30
Asp Met His Trp Val Arg Gln Thr Thr Gly Lys Gly Leu Glu Trp Val
 35          40          45
Ser Gly Ile Gly Thr Ala Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
 50          55          60
Gly Arg Phe Thr Ile Ser Arg Glu Asp Ala Lys Asn Ser Leu Tyr Leu
 65          70          75          80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
 85          90          95
Arg Val Gly Tyr Asp Trp Asn Phe Val Ala Phe Asp Tyr Trp Gly Gln
100         105         110
Gly Thr Leu Val Thr Val Ser Ser
115         120

```

```

<210> SEQ ID NO 67
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 67

ggattcacct tcagtagtta cgac

```

```

<210> SEQ ID NO 68
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 68

Gly Phe Thr Phe Ser Ser Tyr Asp
 1           5

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-continued

<210> SEQ ID NO 69
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 69

atggtaactg ctggagatac a

21

<210> SEQ ID NO 70
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 70

Ile Gly Thr Ala Gly Asp Thr
1 5

<210> SEQ ID NO 71
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 71

gcaagagtgg gatatgactg gaacctcgct gcatttgcac ac

42

<210> SEQ ID NO 72
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 72

Ala Arg Val Gly Tyr Asp Trp Asn Phe Val Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 73
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 73

gatattgtga tgactcagtc tccactctcc ctgccccgtca cccctggaga gccggccctcc 60
atctcctgca ggtcttagtca gagccctctg catagtaatg gataacaacta tttggattgg 120
tacctgcaga agccaggggca gtcgcacag ctcctgatcc acttgggtctc tattcgggcc 180
tccgggggtcc ctgacaggtt cagtggcagt ggatcaggca cagatttac acttaaaatc 240
agcagagtggtt aggctgagga tggtggatt tattactgca tgcaagctct tc当地actccg 300
tggacgttgc gccaaggggac caaggtggaa atcaaa 336

<210> SEQ ID NO 74
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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-continued

<400> SEQUENCE: 74

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
1				5				10				15			

Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser
				20		25				30					

Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
					35	40			45						

Pro	Gln	Leu	Leu	Ile	His	Leu	Val	Ser	Ile	Arg	Ala	Ser	Gly	Val	Pro
					50	55			60						

Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
					65	70		75		80					

Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Ile	Tyr	Tyr	Cys	Met	Gln	Ala
					85		90		95						

Leu	Gln	Thr	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys
					100		105			110					

<210> SEQ ID NO 75

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 75

cagagcctcc tgcatagtaa tggatacaac tat 33

<210> SEQ ID NO 76

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 76

Gln	Ser	Leu	Leu	His	Ser	Asn	Gly	Tyr	Asn	Tyr
1				5				10		

<210> SEQ ID NO 77

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 77

ttggtctct 9

<210> SEQ ID NO 78

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 78

Leu	Val	Ser
1		

<210> SEQ ID NO 79

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 79

atgcaagctc ttcaaactcc gtggacg

27

<210> SEQ_ID NO 80
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 80

Met Gln Ala Leu Gln Thr Pro Trp Thr
 1 5

<210> SEQ_ID NO 81
 <211> LENGTH: 357
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 81

cagggtgcagc tgcaggagtc gggcccagga ctgggtgaagc cttcacagac cctgtccctc	60
accttgcactg tctctgggtgg ctccgtcagc agtggtgatt actactggag ctggatccgc	120
cagcaccagg ggaaggggct ggactggatt gggcacatct attacagtgg gagcacctac	180
tacaacccgt ccctcaagag tcgagttacc atatcactag acacgtctaa gaaccaggc	240
tccctgaagc tgaactctgt gactgccgac gacacggccg tgtattactg tgcgagaacg	300
gtataactg gaactatgga ctactggggc cagggaaacc cgggtcaccgt ctccctca	357

<210> SEQ_ID NO 82
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 82

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Val Ser Ser Gly
 20 25 30

Asp Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Asp
 35 40 45

Trp Ile Gly His Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe
 65 70 75 80

Ser Leu Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Thr Ala Ile Thr Gly Thr Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ_ID NO 83
 <211> LENGTH: 30

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 83

ggtgtggctccg tcagcagtgg tgattactac

30

<210> SEQ ID NO 84
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 84

Gly	Gly	Ser	Val	Ser	Ser	Gly	Asp	Tyr	Tyr
1				5					10

<210> SEQ ID NO 85
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 85

atcttattaca gtgggagcac c

21

<210> SEQ ID NO 86
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 86

Ile	Tyr	Tyr	Ser	Gly	Ser	Thr
1				5		

<210> SEQ ID NO 87
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 87

gcgagaacgg ctataactgg aactatggac tac

33

<210> SEQ ID NO 88
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 88

Ala	Arg	Thr	Ala	Ile	Thr	Gly	Thr	Met	Asp	Tyr
1				5					10	

<210> SEQ ID NO 89
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 89

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gaaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctgcagggga gagagccacc      60
ctctcctgca gggccagtca gagtgtagc agcaacttag cctggttcca gcagaaacct      120
ggccaggctc ccagggctt catctatgtat gcatctacca gggccactgg catcccagcc      180
aggttcagtg gcagtgggtc tgggacagag ttcactctca tcatcagcag cctgcagtct      240
gaagattttg cacttattta ctgtcagcag tataatagct ggtggacgtt cggccaaggg      300
accaagggtgg aaatcaaa                                              318

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<210> SEQ ID NO 90

<211> LENGTH: 106

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 90

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Ala Gly
 1           5          10          15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20          25          30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35          40          45
Tyr Asp Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50          55          60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Ser
 65          70          75          80
Glu Asp Phe Ala Leu Tyr Tyr Cys Gln Gln Tyr Asn Ser Trp Trp Thr
 85          90          95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100         105

```

<210> SEQ ID NO 91

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 91

cagagtgtta gcagcaac 18

<210> SEQ ID NO 92

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 92

Gln Ser Val Ser Ser Asn
 1 5

<210> SEQ ID NO 93

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 93

gatgcacatc

9

<210> SEQ ID NO 94
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 94

Asp Ala Ser

1

<210> SEQ ID NO 95
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 95

cagcagtata atagctggtg gacg

24

<210> SEQ ID NO 96
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 96

Gln Gln Tyr Asn Ser Trp Trp Thr

1 5

<210> SEQ ID NO 97
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 97

gagggtgcagc tgggtggagtc tgggggaggc ttgggtgcagc ctggcggttc cctgagactc	60
tccctgtgcag cctctggatt cacctttgat gatTTTgcca ttcaCTGggT ccggcaaaACT	120
ccagggggg gcctggagtg ggtctcaggt cttagttggaa atagtgcTTA catAGCCTAT	180
gcccactctg tgaaggggccg attcaccatc tccagagaca acggcaagga ctccctctat	240
ctgcAAATGA acagtctgag acctgaggac acggcCTTGT attactgtgt aaaAGATAca	300
gacatacacc ttggTTTCT ctTGactTC tggggccagg gaaccCTGgt caccgtctcc	360
tca	363

<210> SEQ ID NO 98
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 98

Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Gly

1

5

10

15

-continued

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Phe
20 25 30

Ala Ile His Trp Val Arg Gln Thr Pro Gly Arg Gly Leu Glu Trp Val
35 40 45

Ser Gly Leu Ser Trp Asn Ser Ala Tyr Ile Ala Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asp Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Val Lys Asp Thr Asp Ile His Leu Trp Phe Leu Phe Asp Phe Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 99
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 99

ggattcacct ttgatgattt tgcc

24

<210> SEQ ID NO 100
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 100

Gly Phe Thr Phe Asp Asp Phe Ala
1 5

<210> SEQ ID NO 101
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 101

cttagttgga atagtgccta cata

24

<210> SEQ ID NO 102
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 102

Leu Ser Trp Asn Ser Ala Tyr Ile
1 5

<210> SEQ ID NO 103
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 103

gtaaaagata cagacataca cctttggttt ctcttgact tc 42

<210> SEQ ID NO 104
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 104

Val Lys Asp Thr Asp Ile His Leu Trp Phe Leu Phe Asp Phe
1 5 10

<210> SEQ ID NO 105
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 105

gacatccaga tgacctcgtc tccttcacc ctgtctgcat ctgttaggaga cagagtacc	60
atcaacttgc gggccaggta gagtattagt agttgggtgg cctggtatca acagaaaacca	120
ggaaaaagccc ctaaactcct gatctataag gcgtcttagtt tagaaaagtgg ggtccccatcg	180
aggttcagcg gcagtggatc tggcacagaa ttcaactctca ccatcagcag cctgcagcct	240
gatgattttg caacttatta ctgccaacaa tataatagtt attcgacgtt cggccaaggg	300
acacgactgg agattaaa	318

<210> SEQ ID NO 106
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 106

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile
35 40 45Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Thr
85 90 95Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> SEQ ID NO 107
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 107

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cagagtatta gtagttgg 18

<210> SEQ ID NO 108
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 108

Gln Ser Ile Ser Ser Trp
1 5

<210> SEQ ID NO 109
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 109

aaggcgtct 9

<210> SEQ ID NO 110
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 110

Lys Ala Ser
1

<210> SEQ ID NO 111
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 111

caacaatata atagttattc gacg 24

<210> SEQ ID NO 112
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 112

Gln Gln Tyr Asn Ser Tyr Ser Thr
1 5

<210> SEQ ID NO 113
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 113

gaggtgcagc tggtgaggc tgggggaggc ttggtaacgc ctggggggc cctgagactc 60

tcctgtcgac cctctggatt cacctttagc agctatgaca tgagctgggt ccgccaggt 120

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ccagggaaagg ggctggagtg ggtctcaggt atcagtggta gtggagatag cacataactac      180
gcaggctccg tgaagggccg gtccaccatc tccagagaca attccaagaa cactctgtat      240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gtatgactac      300
agtaactact gggaccacta cggttatggac gtctggggcc aagggaccac ggtcaccgtc      360
tcctca                                         366

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<210> SEQ ID NO 114

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 114

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1							5		10				15		

Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
								20		25			30		

Asp	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
								35		40		45			

Ser	Gly	Ile	Ser	Gly	Ser	Gly	Asp	Ser	Thr	Tyr	Tyr	Ala	Gly	Ser	Val
								50		55		60			

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
								65		70		75		80	

Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
								85		90		95			

Ala	Tyr	Asp	Tyr	Ser	Asn	Tyr	Trp	Asp	His	Tyr	Gly	Met	Asp	Val	Trp
								100		105		110			

Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser						
								115		120					

<210> SEQ ID NO 115

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 115

ggattcacct ttagcagcta tgac 24

<210> SEQ ID NO 116

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 116

Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Asp
1						5	

<210> SEQ ID NO 117

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 117

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atcagtggta gtggagatag caca 24

<210> SEQ ID NO 118
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 118

Ile Ser Gly Ser Gly Asp Ser Thr
1 5

<210> SEQ ID NO 119
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 119

gcgtatgact acagtaacta ctgggaccac tacggatgg acgtc 45

<210> SEQ ID NO 120
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 120

Ala Tyr Asp Tyr Ser Asn Tyr Trp Asp His Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 121
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 121

gacatecaga tgacctcagtc tccttccacc ctgtctgcat ctgttaggaga cagagtccacc 60
atcaacttgcc gggccagtcgca gagtattagt agctggttgg cctggtatca gcagaaacca 120
ggaaaagccc ctaagctcct gatctataag gcgctctaggtagt tagaaagtgg ggtccccatca 180
aggttcagcg gcagtggtatc tgggacagaa ttcaactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tataatactt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 122
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 122

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

-continued

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Thr Tyr Ser Arg
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 123
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 123

cagagtatta gtagctgg 18

<210> SEQ ID NO 124
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 124

Gln Ser Ile Ser Ser Trp
 1 5

<210> SEQ ID NO 125
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 125

aaggcggtct 9

<210> SEQ ID NO 126
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 126

Lys Ala Ser
 1

<210> SEQ ID NO 127
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 127

caaacagtata atacttattc tcggacg 27

<210> SEQ ID NO 128

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<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 128

Gln Gln Tyr Asn Thr Tyr Ser Arg Thr
1 5

<210> SEQ ID NO 129
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 129

caggtgcagc tgcaggagtc gggcccgagga ctggtaagc cttcacagac cctgtccctc	60
acctgcactg tctctgggtgg ctccatcagc agtgggtatt actactggaa ctggatccgc	120
cagtaccacag ggaagggcct ggagttgatt ggctacatct attacagtgg aatcacctac	180
tacaacccgt ccctcaagag tcgacttacc atttcatttag acacgtctaa gaaccagttc	240
tccctgaagc tgagttctgt gactgccgac gacacggccg tgtattactg tgcgagagat	300
agagtggaaac tacgggcttt tgatatctgg ggccaaggaa caatggcac cgtctttca	360

<210> SEQ ID NO 130
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 130

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Asp Tyr Tyr Trp Asn Trp Ile Arg Gln Tyr Pro Gly Lys Gly Leu Glu
35 40 45

Leu Ile Gly Tyr Ile Tyr Tyr Ser Gly Ile Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 131
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 131

ggtgtggctcca tcagcagtgg tgattactac

30

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<210> SEQ ID NO 132
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 132

Gly Gly Ser Ile Ser Ser Gly Asp Tyr Tyr
1 5 10

<210> SEQ ID NO 133
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 133

atcttattaca gtggaatcac c

21

<210> SEQ ID NO 134
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 134

Ile Tyr Tyr Ser Gly Ile Thr
1 5

<210> SEQ ID NO 135
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 135

gcgagagata gagtgaaact acgggcttt gatatc

36

<210> SEQ ID NO 136
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 136

Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 137
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 137

gacatccaga tgaccaggc tccatcctcc ctgtctgcat ctgttaggaga cagagtccacc 60

atcacttgcc aggcgagtca ggacattagt aactattaa attggtatca gcagaaaccca 120

gggaaagccc ctaaactcct gatcaacgat gcatccaatt tggaaacagg ggtccccatca 180

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aggttcagtg gaagtggatc tggacagat ttacttca ccatcagcag cctgcagcct	240
gaagatattg caacatatta ctgtcaacat tatgatagtc tccctctcac ctccggccaa	300
gggacacgac tggagattaa a	321

<210> SEQ ID NO 138
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 138

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly			
1	5	10	15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr			
20	25	30	
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile			
35	40	45	
Asn Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly			
50	55	60	
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro			
65	70	75	80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Tyr Asp Ser Leu Pro Leu			
85	90	95	
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys			
100	105		

<210> SEQ ID NO 139
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 139

caggacatta gtaactat	18
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<210> SEQ ID NO 140
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 140

Gln Asp Ile Ser Asn Tyr	
1	5

<210> SEQ ID NO 141
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 141

gatgcattc	9
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<210> SEQ ID NO 142
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 142

Asp Ala Ser
 1

<210> SEQ ID NO 143
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 143

caacattatg atagtctccc ttcacc

27

<210> SEQ ID NO 144
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 144

Gln His Tyr Asp Ser Leu Pro Leu Thr
 1 5

<210> SEQ ID NO 145
 <211> LENGTH: 360
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 145

cagggtgcagc tgcaggagtc gggcccgagga ctgggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctgggtgg ctccatcagc agtgggtgatt actactggaa ctggatccgc	120
cagtaaccag ggaaggccct ggagggtgatt ggctacatct attacagtgg aatcacctac	180
tacaaccctgt ccctcaagag tcgacttacc atttcatttag acacgtctaa gaaccaggatc	240
tcctgtggc tgagttctgt gactgccgag gacacggccg tgtattactg tgcgagagat	300
agagtggaac tacgagctt tgatatctgg ggccaaggga caatggtcac cgtctctca	360

<210> SEQ ID NO 146
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 146

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
 20 25 30

Asp Tyr Tyr Trp Asn Trp Ile Arg Gln Tyr Pro Gly Lys Gly Leu Glu
 35 40 45

Leu Ile Gly Tyr Ile Tyr Tyr Ser Gly Ile Thr Tyr Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe
 65 70 75 80

-continued

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 147
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 147

ggtggtccca tcagcagtgg tgattactac 30

<210> SEQ ID NO 148
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 148

Gly Gly Ser Ile Ser Ser Gly Asp Tyr Tyr
1 5 10

<210> SEQ ID NO 149
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 149

atcttattaca gtggaatcac c 21

<210> SEQ ID NO 150
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 150

Ile Tyr Tyr Ser Gly Ile Thr
1 5

<210> SEQ ID NO 151
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 151

gcgagagata gagtggaaact acgagcttt gatatc 36

<210> SEQ ID NO 152
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 152

```

Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile
 1           5           10

```

<210> SEQ ID NO 153

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 153

```

gacatccaga tgaccaggc tccatccctcc ctgtctgcat ctataggaga cagaatcacc      60
atctcttgcc aggcgagtc ggcacattaac aactattaa attggatataca gcagaaaccca      120
gggaaaagccc ctaaaactcct gatctacgtat gcatccaatt tggaaacagg gatcccatca      180
aggttcaagtg gaagtggatc tgggacagat tttactttca ccatcagccg cctgcagcct      240
gaagatattg caacatatta ctgtcaaacac tatgatagtc tccctctcac cttcgccaa      300
gggacacgac tggagattaa a                                         321

```

<210> SEQ ID NO 154

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 154

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Ile Gly
 1           5           10          15

```

```

Asp Arg Ile Thr Ile Ser Cys Gln Ala Ser Gln Asp Ile Asn Asn Tyr
 20          25          30

```

```

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35          40          45

```

```

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Ile Pro Ser Arg Phe Ser Gly
 50          55          60

```

```

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Gly Leu Gln Pro
 65          70          75          80

```

```

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Tyr Asp Ser Leu Pro Leu
 85          90          95

```

```

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
 100         105

```

<210> SEQ ID NO 155

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 155

caggacatta acaactat

18

<210> SEQ ID NO 156

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 156

Gln Asp Ile Asn Asn Tyr
 1 5

<210> SEQ ID NO 157
 <211> LENGTH: 9
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 157

gatgcattcc

9

<210> SEQ ID NO 158
 <211> LENGTH: 3
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 158

Asp Ala Ser
 1

<210> SEQ ID NO 159
 <211> LENGTH: 27
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 159

caacactatg atagtctccc ttcacc

27

<210> SEQ ID NO 160
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 160

Gln His Tyr Asp Ser Leu Pro Leu Thr
 1 5

<210> SEQ ID NO 161
 <211> LENGTH: 360
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 161

caggtgcagc tgcaggagtc gggcccagga ctgggtatgc cttcacagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcaac agtggtgatt actactggaa ctggatccgc	120
cagcacccag ggaaggccct ggagtggatt ggatacatct attacagtga aatcgttat	180
cacaacccgt ccctaagag tcgagttacc acctaatacg acacgtctac gaaccaggta	240
tccctgaagc tgagctctgt gactgcccg gacacggccg tctattactg tgcgagagat	300
agagtggaaac tacgagcttt tgatatatctgg ggccaaggga caatggtcac cgtctttca	360

<210> SEQ ID NO 162

US 9,132,192 B2

95**96**

-continued

<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 162

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Met	Pro	Ser	Gln
1				5				10					15		

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Gly
20 25 30

Asp Tyr Tyr Trp Asn Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Ser Glu Ile Ser Tyr His Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Thr Ser Ile Asp Thr Ser Thr Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 163
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 163

ggtggttccca tcaacagtgg tgattactac 30

<210> SEQ ID NO 164
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 164

Gly Gly Ser Ile Asn Ser Gly Asp Tyr Tyr
1 5 10

<210> SEQ ID NO 165
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 165

atcttattaca gtgaaatcag t 21

<210> SEQ ID NO 166
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 166

-continued

Ile Tyr Tyr Ser Glu Ile Ser
1 5

<210> SEQ ID NO 167
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 167

gcgagagata gagtggaaact acgagcttt gatatac 36

<210> SEQ ID NO 168
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 168

Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 169
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 169

gacatccaga tgaccaggc tccatccccc ctgtctgcat ctgttaggaga cagagtccacc 60
atcaacttgcc aggcgagtc ggacatttgc aactatttaa atggatcatca gcagaaaccca 120
gggaaagccc ctaaactcct gatctacgt gcatccaattt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tggcacat tttactttca ccatcagcag cctgcagcct 240
gaagatattt caacatatta ctgtcaaacat tatgatagtc tccctctcac cttcgccaa 300
gggacacgac tggagattaa a 321

<210> SEQ ID NO 170
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 170

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Tyr Asp Ser Leu Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys

-continued

100

105

<210> SEQ ID NO 171
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 171

caggacattat

18

<210> SEQ ID NO 172
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 172

Gln Asp Ile Ser Asn Tyr
1 5

<210> SEQ ID NO 173
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 173

gatgcattcc

9

<210> SEQ ID NO 174
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 174

Asp Ala Ser
1

<210> SEQ ID NO 175
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 175

caacactatg atagtctccc tctcacc

27

<210> SEQ ID NO 176
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 176

Gln His Tyr Asp Ser Leu Pro Leu Thr
1 5

<210> SEQ ID NO 177

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<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 177

caggtgcagc tgcaggagtc gggcccagga ctggtgatgc cttcacagac cctgtccctc      60
acctgcactg tctctgggtgg ctccatcaac agtgggtatt actactggaa ctggatccgc      120
cagcacccag ggaaggggct ggagtggatt ggatacatct attacagtga aatcagttat      180
cacaaccctg ccctcaagag tcgagttacc acctcaatag acacgtctac gaaccaggta      240
tccctgaagc tgagctctgt gactgcccgcg gacacggccg tctattactg tgcgagagat      300
agagtggaaac tacgagctt tgatatctgg ggccaaggga caatggtac cgtctcttca      360

```

```

<210> SEQ ID NO 178
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 178

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Met Pro Ser Gln
 1           5          10          15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Gly
 20          25          30

Asp Tyr Tyr Trp Asn Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
 35          40          45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Glu Ile Ser Tyr His Asn Pro Ser
 50          55          60

Leu Lys Ser Arg Val Thr Thr Ser Ile Asp Thr Ser Thr Asn Gln Phe
 65          70          75          80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85          90          95

Cys Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile Trp Gly Gln
100         105         110

Gly Thr Met Val Thr Val Ser Ser
115          120

```

```

<210> SEQ ID NO 179
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 179

ggtggctcca tcaacagtgg tgattactac          30

```

```

<210> SEQ ID NO 180
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 180

Gly Gly Ser Ile Asn Ser Gly Asp Tyr Tyr
 1           5          10

```

-continued

<210> SEQ ID NO 181
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 181

atcttattaca gtgaaatcag t

21

<210> SEQ ID NO 182
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 182

Ile Tyr Tyr Ser Glu Ile Ser
1 5

<210> SEQ ID NO 183
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 183

gcgagagata gagtgaaact acgagcttt gatatac

36

<210> SEQ ID NO 184
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 184

Ala Arg Asp Arg Val Glu Leu Arg Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 185
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 185

gacatccaga tgacctcagtc tccatccccc ctgtctgcat ctgttggaga cagagtccacc 60
atcacttgcc aggcgagtca ggacatttagc aactatttaa attggttatca gcagaaacca 120
ggaaaagccc ottaaactcct gatctacgt gcatccaatt tggagacagg ggtcccatca 180
aggttcagtg gaagtggatc tggcacatgt tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacatatta ctgtcaacac tatgatagtc tccctctcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> SEQ ID NO 186
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 186

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1					5			10						15	

Asp	Arg	Val	Thr	Ile	Thr	Cys	Gln	Ala	Ser	Gln	Asp	Ile	Ser	Asn	Tyr
	20					25								30	

Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
				35		40						45			

Tyr	Asp	Ala	Ser	Asn	Leu	Glu	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55				60					

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70			75						80	

Glu	Asp	Ile	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Tyr	Asp	Ser	Leu	Pro	Leu
	85					90						95			

Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys					
	100					105									

<210> SEQ_ID NO 187

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 187

caggacattt gcaactat

18

<210> SEQ_ID NO 188

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 188

Gln	Asp	Ile	Ser	Asn	Tyr
1				5	

<210> SEQ_ID NO 189

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 189

gatgcattcc

9

<210> SEQ_ID NO 190

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 190

Asp	Ala	Ser
1		

<210> SEQ_ID NO 191

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 191

caacactatg atagtctccc tctcacc

27

<210> SEQ ID NO 192

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 192

Gln His Tyr Asp Ser Leu Pro Leu Thr
 1 5

<210> SEQ ID NO 193

<211> LENGTH: 384

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 193

gagggtgcagc	tggtgagtc	tgggggaggc	gtggtagc	cggggggc	cctgagactc	60
tccctgtcgag	cctctggatt	cacctttat	gattatgcc	tgcactgggt	ccgtcaagct	120
ccagggaaagg	gtctggagtg	ggtctctttt	attagtgggg	atgggtggtag	cacatactat	180
gcagactctg	tgaaggggccg	attcaccatc	tccagagaca	acagaaaaaa	ctccctgtat	240
ctgcaaatga	acagtctgag	aactgaggac	accgccttgt	attactgtgc	aaaaaattat	300
gatagtagtg	gttattacta	cccttactac	tactactacg	gtatggacgt	ctggggccaa	360
gggaccacgg	tcaccgtctc	ctca				384

<210> SEQ ID NO 194

<211> LENGTH: 128

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 194

Glu Val Gln Leu Val Glu Ser Gly Gly Val Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
 20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Leu Ile Ser Gly Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Ser Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95

Ala Lys Asn Tyr Asp Ser Ser Gly Tyr Tyr Pro Tyr Tyr Tyr Tyr
 100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

-continued

<210> SEQ ID NO 195
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 195

ggattcacct ttgatgatta tgcc

24

<210> SEQ ID NO 196
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 196

Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> SEQ ID NO 197
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 197

attagtgggg atgggttag caca

24

<210> SEQ ID NO 198
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 198

Ile Ser Gly Asp Gly Gly Ser Thr
1 5

<210> SEQ ID NO 199
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 199

gcaaaaaatt atgatagtag tggtttattac tacccttact actactacta cggttatggac

60

gtc

63

<210> SEQ ID NO 200
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 200

Ala Lys Asn Tyr Asp Ser Ser Gly Tyr Tyr Tyr Pro Tyr Tyr Tyr Tyr
1 5 10 15Tyr Gly Met Asp Val
20

-continued

<210> SEQ ID NO 201
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 201

```
gacatccaga tgacctcacc ctgtctgcat ctgttaggaga cagagtccacc      60
atcaacttgc gggccagtc gagtattagt agctggtagg cctggtatca gcagaaacca    120
ggaaaagccc ctaagctcct gatctataag gcgtcttagct tagaaagtgg ggtcccatca    180
aggttcagcg gcagtggtatc tggacagaa ttcaacttcata ccatcagtag cctgcagcct    240
gtatgttttgc caacttattat cttccaaacag tataatagttt attctcgac gttcggccaa    300
gggaccaagg tggaaatcaa a                                         321
```

<210> SEQ ID NO 202
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 202

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1           5          10          15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
 20          25          30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35          40          45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50          55          60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65          70          75          80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Arg
 85          90          95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100         105
```

<210> SEQ ID NO 203
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 203

```
cagagtatta gtagctgg                                         18
```

<210> SEQ ID NO 204
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 204

```
Gln Ser Ile Ser Ser Trp
 1           5
```

-continued

<210> SEQ ID NO 205
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 205

aaggcgtct

9

<210> SEQ ID NO 206
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 206

Lys Ala Ser
1

<210> SEQ ID NO 207
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 207

caacagtata atagttattc tcggacg

27

<210> SEQ ID NO 208
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 208

Gln Gln Tyr Asn Ser Tyr Ser Arg Thr
1 5

<210> SEQ ID NO 209
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 209

gaggtgcagc tggggagtc gggcccgagga ctgggtgcagc cttcacagac cctgtccctc	60
acctgcactg tctctgggtgg ctccatcaac agtgggtatt tctactggag ttggatccgc	120
cagcatccag ggaaggccct ggagtggatt ggtcacatat attacagtgg gatcacctac	180
tacagtccgt ccctcaagag tcgacttacc atctcagtag acacgtctaa gaaccagttc	240
tccctgaagc tgagttctgt gactgccgac gacacggccg tgtattactg tgcgagaaaag	300
agggttaactg gggaaagttga ctactggggc cagggaaaccc tggtcaccgt ctccctca	357

<210> SEQ ID NO 210
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 210

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Pro	Gly	Leu	Val	Gln	Pro	Ser	Gln
1					5			10					15		

Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Asn	Ser	Gly
					20			25				30			

Asp	Phe	Tyr	Trp	Ser	Trp	Ile	Arg	Gln	His	Pro	Gly	Lys	Gly	Leu	Glu
					35		40				45				

Trp	Ile	Gly	His	Ile	Tyr	Tyr	Ser	Gly	Ile	Thr	Tyr	Tyr	Ser	Pro	Ser
					50		55		60						

Leu	Lys	Ser	Arg	Leu	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe
65						70		75				80			

Ser	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr
					85			90			95				

Cys	Ala	Arg	Lys	Arg	Val	Thr	Gly	Glu	Val	Asp	Tyr	Trp	Gly	Gln	Gly
					100			105			110				

Thr	Leu	Val	Thr	Val	Ser	Ser									
					115										

<210> SEQ_ID NO 211

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 211

ggtggtccca tcaacagtgg tgatttctac

30

<210> SEQ_ID NO 212

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 212

Gly	Gly	Ser	Ile	Asn	Ser	Gly	Asp	Phe	Tyr
1				5			10		

<210> SEQ_ID NO 213

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 213

atatattaca gtgggatcac c

21

<210> SEQ_ID NO 214

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 214

Ile	Tyr	Tyr	Ser	Gly	Ile	Thr
1					5	

<210> SEQ_ID NO 215

<211> LENGTH: 33

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 215

gcgagaaaaga gggtaactgg ggaagttgac tac

33

<210> SEQ ID NO 216
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 216

Ala Arg Lys Arg Val Thr Gly Glu Val Asp Tyr
1 5 10

<210> SEQ ID NO 217
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 217

gacatccaga tgacctcagtc tccatccctcc ctgtctgcat ctgttaggaga cagaatcacc	60
atcacttgcc aggcgaatca ggacattaac aactattaa attggatatca gcaaaaggcca	120
gggaaagccc ctaagctcct gatctccat gcatccaatt tggaaacagg ggtcccatca	180
agattcagtg gaagtggatc tggacagat ttactttca ccatcagcag cctgcagcct	240
gaagatattg caacatatta ctgtcaacag tatgataatc tccctccac cttcgccaa	300
gggacacgac tggagattaa acga	324

<210> SEQ ID NO 218
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 218

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15Asp Arg Ile Thr Ile Thr Cys Gln Ala Asn Gln Asp Ile Asn Asn Tyr
20 25 30Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45Ser Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Pro
85 90 95Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
100 105

<210> SEQ ID NO 219
<211> LENGTH: 18
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 219

caggacatta acaactat

18

<210> SEQ ID NO 220
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 220

Gln Asp Ile Asn Asn Tyr
1 5

<210> SEQ ID NO 221
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 221

gatgcattcc

9

<210> SEQ ID NO 222
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 222

Asp Ala Ser
1

<210> SEQ ID NO 223
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 223

caacagtatg ataatctccc tccccacc

27

<210> SEQ ID NO 224
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 224

Gln Gln Tyr Asp Asn Leu Pro Pro Thr
1 5

<210> SEQ ID NO 225
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 225

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caggtgcagc tgcaggagtc gggcccgaga ctggtaacc cttcacagac cctgtccctc      60
acctgcactg tctctggtgg ctccatcaat agtggtgatt actactggag ctgggtccgc     120
cagcacccag ggaagggcct ggagtggatt ggatacatct attacagtgg gagcacctac     180
tacaacccgt ccctaagag tcgagttacc atctcagtgg acacgtctaa gaaccaggtc     240
tccctgaaac ttagctctgt gactgtcgcg gacacggccg tataattactg tgcgagatg     300
ggctacagta aagggtactt tgactcctgg ggccagggaa ccctggtcac tgtctccctca   360
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<210> SEQ ID NO 226

<211> LENGTH: 120

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 226

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Asn	Pro	Ser	Gln
1				5			10				15				

Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Asn	Ser	Gly
			20				25				30				

Asp	Tyr	Tyr	Trp	Ser	Trp	Val	Arg	Gln	His	Pro	Gly	Lys	Gly	Leu	Glu
			35			40					45				

Trp	Ile	Gly	Tyr	Ile	Tyr	Tyr	Ser	Gly	Ser	Thr	Tyr	Tyr	Asn	Pro	Ser
	50				55					60					

Leu	Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe
65				70				75				80			

Ser	Leu	Lys	Leu	Ser	Ser	Val	Thr	Val	Ala	Asp	Thr	Ala	Val	Tyr	Tyr
	85					90					95				

Cys	Ala	Arg	Val	Gly	Tyr	Ser	Lys	Gly	Tyr	Phe	Asp	Ser	Trp	Gly	Gln
	100				105					110					

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
		115				120									

<210> SEQ ID NO 227

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 227

ggtgtggctcca	tcaatagtgg	tgattactac													30
--------------	------------	------------	--	--	--	--	--	--	--	--	--	--	--	--	----

<210> SEQ ID NO 228

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 228

Gly	Gly	Ser	Ile	Asn	Ser	Gly	Asp	Tyr	Tyr						
1			5			10									

<210> SEQ ID NO 229

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Tyr Lys Ser Tyr Trp Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ_ID NO 235

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 235

gagagtatta gtagctgg

18

<210> SEQ_ID NO 236

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 236

Glu Ser Ile Ser Ser Trp
1 5

<210> SEQ_ID NO 237

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 237

gatgcgtct

9

<210> SEQ_ID NO 238

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 238

Asp Ala Ser
1

<210> SEQ_ID NO 239

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 239

caacagtata aaagttattg gacg

24

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<210> SEQ ID NO 240
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 240
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Gln Gln Tyr Lys Ser Tyr Trp Thr
1 5

```
<210> SEQ ID NO 241
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 241

cagggtgcagc	tgggtggagtc	tgggggaggc	gtgggtccagc	ctgggaagtc	cctgagactc	60
tccctgtgcag	cctctggatt	caccttca	gtatggca	tgaactgggt	ccgcaggct	120
ccaggcaagg	ggctggactg	ggtggcagtt	atttcagat	atggaaagtaa	taaagactat	180
gtggactccg	tgaggggtcg	attcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
ctgcaaatga	acagcctgag	cgctgaagac	acggctgtct	attactgtgc	gaaagatcgt	300
atcaactggca	ctcattacta	cggtttgac	gtctggggc	aagggaccac	ggtcaccgtc	360
ttccatca						366

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<210> SEQ ID NO 242
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 242

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Lys
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ile Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
35 40 45

Ala Val Ile Ser Asp Asp Gly Ser Asn Lys Asp Tyr Val Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Ser Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Ile Thr Gly Thr His Tyr Tyr Gly Leu Asp Val Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

```
<210> SEQ ID NO 243
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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<400> SEQUENCE: 243

ggattcacct tcagtatcta tggc

24

<210> SEQ_ID NO 244
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 244

Gly Phe Thr Phe Ser Ile Tyr Gly
1 5

<210> SEQ_ID NO 245
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 245

atttcagatg atggaagtaa taaa

24

<210> SEQ_ID NO 246
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 246

Ile Ser Asp Asp Gly Ser Asn Lys
1 5

<210> SEQ_ID NO 247
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 247

gcgaaaagtc gtatcactgg cactcattac tacgggttgg acgtc

45

<210> SEQ_ID NO 248
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 248

Ala Lys Asp Arg Ile Thr Gly Thr His Tyr Tyr Gly Leu Asp Val
1 5 10 15

<210> SEQ_ID NO 249
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 249

gacatccaga tgaccaggc tccgtcctca ctgtctgcat ctgtcgagaa cagaatcacc

60

-continued

atcacttgc gggcgagtca ggacattgcc aattattnag cctggttca gcagaaacca	120
ggttaatgcc ctacgtccct gatctatgct gcatccatt tgcaaagtgg ggtcccatca	180
aagttcagcg gcagtggtac tggacagat ttcactctca ccatcaccag cctgcagcca	240
gaagatttt caagttatta ctgccaacaa tataatagaa agccgtggac gttcggccga	300
gggaccaagg tggaaatcaa a	321

<210> SEQ ID NO 250
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 250

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly			
1	5	10	15
Asp Arg Ile Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ala Asn Tyr			
20	25	30	
Leu Ala Trp Phe Gln Gln Lys Pro Gly Asn Ala Pro Thr Ser Leu Ile			
35	40	45	
Tyr Ala Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly			
50	55	60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Leu Gln Pro			
65	70	75	80
Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Tyr Asn Arg Lys Pro Trp			
85	90	95	
Thr Phe Gly Arg Gly Thr Lys Val Glu Ile Lys			
100	105		

<210> SEQ ID NO 251
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 251

caggacattg ccaattat 18

<210> SEQ ID NO 252
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 252

Gln Asp Ile Ala Asn Tyr
1 5

<210> SEQ ID NO 253
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 253

gctgcattc 9

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<210> SEQ ID NO 254
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 254

Ala Ala Ser
1

<210> SEQ ID NO 255
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 255

caacaatata atagaaagcc gtggacg

27

<210> SEQ ID NO 256
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 256

Gln Gln Tyr Asn Arg Lys Pro Trp Thr
1 5

<210> SEQ ID NO 257
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 257

cagggtgcagc tggtgaggc tgggggaggc gtggtccagc ctgggaggc cctgagactc	60
tccctgtcgag cctctggatt caccttcagt atctatggca tgcactgggt ccgccaggct	120
ccaggcaagg gactggagtg ggtgacagtt atatcagacg atggaagtaaaaatactat	180
gttagactccg tgaaggccc attcacccctc tccagagaca attccaagaa cacgctgtat	240
ctgc当地atga acagectgag agctgaggac acggctgtgt attactgtgc gagagatcgt	300
ataactggaa ccaactggta cggtatggac gtctgggccc aggggaccac ggtcaccgtc	360
tccctca	366

<210> SEQ ID NO 258
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 258

Gln Val Gln Leu Val Glu Ser Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ile Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

-continued

35 40 45

Thr Val Ile Ser Asp Asp Gly Ser Lys Lys Tyr Tyr Val Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Leu Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Asp Arg Ile Thr Gly Thr Asn Trp Tyr Gly Met Asp Val Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 259

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 259

ggattcacct tcagtatcta tggc

24

<210> SEQ ID NO 260

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 260

Gly Phe Thr Phe Ser Ile Tyr Gly
 1 5

<210> SEQ ID NO 261

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 261

atatcagacg atgaaatgtaa aaaa

24

<210> SEQ ID NO 262

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 262

Ile Ser Asp Asp Gly Ser Lys Lys
 1 5

<210> SEQ ID NO 263

<211> LENGTH: 45

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 263

gcgagagatc gtataactgg aaccaactgg tacggtatgg acgtc

45

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<210> SEQ ID NO 264
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 264

Ala	Arg	Asp	Arg	Ile	Thr	Gly	Thr	Asn	Trp	Tyr	Gly	Met	Asp	Val
1				5				10				15		

<210> SEQ ID NO 265
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 265

gacatccaga	tgaccaggc	tccatcctca	ctgtctgcat	ctgttaggaga	cagagtccacc	60
atcacttgtc	gggcgagtca	ggacattagc	aattatttag	cctggtttca	gcagaaacca	120
ggaaaagccc	ctaagtccct	gatctttgt	gcatccagg	tgcaaagtgg	gggccccatca	180
aatgttcagcg	gcagtggatc	tggcacagat	ttcactctca	ccatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ctgccaacag	tataatcggt	accattcac	tttcggccct	300
gggacccaaag	tggatatcaa	a				321

<210> SEQ ID NO 266
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 266

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10				15			

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Asn	Tyr
		20					25				30				

Leu	Ala	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Ser	Leu	Ile
				35		40				45					

Phe	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Gly	Pro	Ser	Lys	Phe	Ser	Gly
			50			55				60					

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70			75			80					

Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Arg	Tyr	Pro	Phe
				85			90			95					

Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile	Lys					
				100		105									

<210> SEQ ID NO 267
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 267

caggacatta gcaattat

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<210> SEQ ID NO 268
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 268

Gln Asp Ile Ser Asn Tyr
1 5

<210> SEQ ID NO 269
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 269

gctgcattcc

9

<210> SEQ ID NO 270
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 270

Ala Ala Ser
1

<210> SEQ ID NO 271
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 271

caacagtata atcggttaccc attcact

27

<210> SEQ ID NO 272
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 272

Gln Gln Tyr Asn Arg Tyr Pro Phe Thr
1 5

<210> SEQ ID NO 273
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 273

cagggtgcagc tgggtggagtc tgggggaggc gtgggtccagc ctggggaggc cctcagactc 60

acctctgtaaag octctgtggatt caccttcagt atctatggca taaactgggt ccgccaggct 120

tcaggcaagg ggctggactg ggtggcagtc atttcagatg atggaagtga taagaagtat 180

gcagattccg tgaaggggccg attcaccatc tcccgagaca attccaaaaa cacggtttat 240

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ctggaaatga	gcagactgag	aagtgaggac	acggctgttt	atttctgtgc	gaaagacccg	300
tttactggaa	accactatta	cggtatggac	gtctggggcc	aagggaccac	ggtcaccgtc	360
tcctca						366

<210> SEQ ID NO 274
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 274

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
1				5			10					15			
Ser	Leu	Arg	Leu	Thr	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ile	Tyr
	20				25							30			
Gly	Ile	Asn	Trp	Val	Arg	Gln	Ala	Ser	Gly	Lys	Gly	Leu	Asp	Trp	Val
	35				40							45			
Ala	Val	Ile	Ser	Asp	Asp	Gly	Ser	Asp	Lys	Lys	Tyr	Ala	Asp	Ser	Val
	50				55							60			
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Val	Tyr
	65				70							80			
Leu	Glu	Met	Ser	Arg	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Phe	Cys
	85					90						95			
Ala	Lys	Asp	Arg	Phe	Thr	Gly	Asn	His	Tyr	Tyr	Gly	Met	Asp	Val	Trp
	100				105							110			
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser						
	115				120										

<210> SEQ ID NO 275
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 275

ggattcacct	tcatgtatcta	tggc		24
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<210> SEQ ID NO 276
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 276

Gly	Phe	Thr	Phe	Ser	Ile	Tyr	Gly
1				5			

<210> SEQ ID NO 277
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 277

atttcagatg	atggaagtga	taag		24
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<210> SEQ ID NO 278
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 278

Ile Ser Asp Asp Gly Ser Asp Lys	
1	5

<210> SEQ ID NO 279
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 279

gcgaaaagacc ggtttactgg aaaccactat tacggatgg acgtc	45
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<210> SEQ ID NO 280
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 280

Ala Lys Asp Arg Phe Thr Gly Asn His Tyr Tyr Gly Met Asp Val			
1	5	10	15

<210> SEQ ID NO 281
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 281

gacatccaga tgacctcagtc tccatcctca ctgtctgcat ctgttaggaga cagagtca	60
atcacttgta gggcgagtca ggacattagc gattatttag cctggttca gcagaaacca	120
ggaaaaagccc ctaagtccct gatctatgtc gcatccattt tgcaaatgg ggtccccatca	180
aggttcagcg gcagtggatc tggacagat ttcaactctca ccatcagcag cctgcagcct	240
gaagattttg ctcttattta ctgtcatcgtataatcggtt tcccgtggac gttcggccaa	300
gggaccaagg tggaaatcaa a	321

<210> SEQ ID NO 282
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 282

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly			
1	5	10	15

Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asp Tyr		
20	25	30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile		
35	40	45

Tyr Ala Ala Ser Ile Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly	
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50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Leu Tyr Tyr Cys His Gln Tyr Asn Arg Phe Pro Trp
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 283
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 283

caggacatttgcgattat 18

<210> SEQ ID NO 284
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 284

Gln Asp Ile Ser Asp Tyr
 1 5

<210> SEQ ID NO 285
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 285

gctgcatacc 9

<210> SEQ ID NO 286
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 286

Ala Ala Ser
 1

<210> SEQ ID NO 287
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 287

catcagttata atcggttccc gtggacg 27

<210> SEQ ID NO 288
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 288

His	Gln	Tyr	Asn	Arg	Phe	Pro	Trp	Thr
1								5

<210> SEQ ID NO 289

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 289

cagggtgcagc	tggtgagtc	tgggggaggc	gtggccagc	ctggggggtc	cctgagactc	60
tctgtgcag	ctctctggatt	cacgttca	gtatctatggca	tacactgggt	ccgccaggct	120
ccaggcaagg	gactggagtg	ggtggcagtc	atatctgtatg	atggaaagttaa	taaaaagtat	180
gcagactccg	tgaaggcccg	attcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
ctgcaaatga	acagcctgag	agctgaggac	acggctataat	tttactgtgc	gaaagatcg	300
ataactggaa	cccactacta	cggaatggac	gtctggggcc	aagggaccac	ggtcaccgtc	360
tcctca						366

<210> SEQ ID NO 290

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 290

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Gly
1															15

Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ile	Tyr
20															30

Gly	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
35															45

Ala	Val	Ile	Ser	Asp	Asp	Gly	Ser	Asn	Lys	Lys	Tyr	Ala	Asp	Ser	Val
50															60

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65															80

Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Ile	Phe	Tyr	Cys
85															95

Ala	Lys	Asp	Arg	Ile	Thr	Gly	Thr	His	Tyr	Tyr	Gly	Met	Asp	Val	Trp
100															110

Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser						
115															120

<210> SEQ ID NO 291

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 291

ggattcacgt tcagtatcta tggc

24

<210> SEQ ID NO 292

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<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 292

Gly Phe Thr Phe Ser Ile Tyr Gly
1 5

<210> SEQ ID NO 293
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 293

atatctgatg atggaagtaa taaa 24

<210> SEQ ID NO 294
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 294

Ile Ser Asp Asp Gly Ser Asn Lys
1 5

<210> SEQ ID NO 295
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 295

gcgaaagatc ggataactgg aacccactac tacggaatgg acgtc 45

<210> SEQ ID NO 296
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 296

Ala Lys Asp Arg Ile Thr Gly Thr His Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 297
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 297

gacatccaga tgaccaggc tccatcccta ctgtctgcat ctgtaggaga cagagttagc 60
atcaacttgtc gggcgagtca ggacattagc aattattna cctggttca gcagaaacca 120
gggaaagccc ctaagtcctt gatctatgct gcttccaggta tgcaaagtgg ggtccatca 180
aaattcagcg gcagtggatc tggatagaa ttcaactctca ccatcagcag cctgcagcct 240

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gaagattttt caacttatta ctgccatcaa tataatcggtt tcccggtggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 298
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 298

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
50 55 60Ser Gly Ser Gly Ile Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80Glu Asp Phe Ser Thr Tyr Tyr Cys His Gln Tyr Asn Arg Phe Pro Trp
85 90 95Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 299
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 299

caggacatta gcaattat 18

<210> SEQ ID NO 300
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 300

Gln Asp Ile Ser Asn Tyr
1 5

<210> SEQ ID NO 301
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 301

gctgcttcc 9

<210> SEQ ID NO 302
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 302

Ala Ala Ser
1

<210> SEQ ID NO 303
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 303

catcaatata atcgttccc gtggacg

27

<210> SEQ ID NO 304
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 304

His Gln Tyr Asn Arg Phe Pro Trp Thr
1 5

<210> SEQ ID NO 305
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 305

gaggtgcagc tggtgaggc tgggggaggc ttggtccagc ctggggggc cctgaggc	60
tcatgtcag cctcttagatt caccttact aactattggc tgagttgggt ccgccaggct	120
ccagggaaagg ggctggaggc ggtggccaaa ataaagcaag atggaaagtga gaaatactat	180
ctggactctg tgaaggaccg attcaccatc tccagagaca acgccaagaa ctcactttat	240
ctgcaaatga acagectgag agccgaggac acggctgtgt attactgtgc gagtagcagc	300
agctggtacg actactacta cggttatggac gtctggggcc acgggaccac ggtcaccgtc	360
tcctca	366

<210> SEQ ID NO 306
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 306

Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Thr Asn Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Lys Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Leu Asp Ser Val
50 55 60

Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Ser Ser Ser Trp Tyr Asp Tyr Tyr Gly Met Asp Val Trp
 100 105 110

Gly His Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 307
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 307

agattcacct ttactaacta ttgg

24

<210> SEQ ID NO 308
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 308

Arg Phe Thr Phe Thr Asn Tyr Trp
 1 5

<210> SEQ ID NO 309
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 309

ataaagcaag atggaagtga gaaa

24

<210> SEQ ID NO 310
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 310

Ile Lys Gln Asp Gly Ser Glu Lys
 1 5

<210> SEQ ID NO 311
 <211> LENGTH: 45
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 311

gcgagtagca gcagctggta cgactactac tacggtatgg acgtc

45

<210> SEQ ID NO 312
 <211> LENGTH: 15
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 312

Ala	Ser	Ser	Ser	Ser	Trp	Tyr	Asp	Tyr	Tyr	Tyr	Gly	Met	Asp	Val
1					5		10				15			

<210> SEQ ID NO 313

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 313

gaaattgtgt	tgactcagtc	tccagacttt	cagtctgtga	ctccaaaaga	gaaagtaccc	60
atcacctgcc	gggcaggta	gaggatttgt	actaacttac	actggtagca	gcagagacca	120
gatcagtctc	caaagctcct	catcaagttt	gcttcccagt	ccttctcagg	ggtcccctcg	180
aggttcagtg	gcagtgatc	tgggacagat	ttcacccctca	ccatcaatag	cctgaaagct	240
gaagatgctg	caacgtattt	ctgtcatcg	actaactttt	tacctcacac	tttcggccga	300
gggaccaagg	tggaaatcaa	acgaa				324

<210> SEQ ID NO 314

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 314

Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Asp	Phe	Gln	Ser	Val	Thr	Pro	Lys
1					5		10		15						

Glu	Lys	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Thr	Asn
		20			25							30			

Leu	His	Trp	Tyr	Gln	Gln	Arg	Pro	Asp	Gln	Ser	Pro	Lys	Leu	Leu	Ile
		35			40							45			

Lys	Phe	Ala	Ser	Gln	Ser	Phe	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
50					55				60						

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asn	Ser	Leu	Glu	Ala
65					70			75		80					

Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	His	Gln	Thr	Asn	Phe	Leu	Pro	His
					85			90		95					

Thr	Phe	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg
					100				105	

<210> SEQ ID NO 315

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 315

cagagcattg gtactaac 18

<210> SEQ ID NO 316

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 316

Gln Ser Ile Gly Thr Asn
1 5

<210> SEQ ID NO 317
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 317

tttgcttcc

9

<210> SEQ ID NO 318
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 318

Phe Ala Ser
1

<210> SEQ ID NO 319
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 319

catcagacta actttttacc tcacact

27

<210> SEQ ID NO 320
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 320

His Gln Thr Asn Phe Leu Pro His Thr
1 5

<210> SEQ ID NO 321
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 321

cagggtgcagc tgggtggagtc tgggggaggc gtgggtccagc ctggggaggtc cctgagactc	60
tccctgtgcag cctctggatt caccttcagt aactatggca tgtactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtgacattc atatcatatg atggaagtaa taaaaactat	180
gttagactcca tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaattga acagtctgag agttgaggac acggctgtat attactgtgc gaaagatcgt	300
ataagtggaa ctccatggta cggttatggac gtctggggcc aagggaccac ggtcaccgtc	360
tcctca	366

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<210> SEQ_ID NO 322
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 322

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1           5           10          15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
 20          25          30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35          40          45

Thr Phe Ile Ser Tyr Asp Gly Ser Asn Lys Asn Tyr Val Asp Ser Met
 50          55          60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65          70          75          80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
 85          90          95

Ala Lys Asp Arg Ile Ser Gly Thr Pro Trp Tyr Gly Met Asp Val Trp
100          105         110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115          120

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<210> SEQ_ID NO 323
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 323

ggattcacct tcagtaacta tggc

24

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<210> SEQ_ID NO 324
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 324

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Gly Phe Thr Phe Ser Asn Tyr Gly
 1           5

```

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<210> SEQ_ID NO 325
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 325

atatcatatg atgaaatgtaa taaa

24

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<210> SEQ_ID NO 326
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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162

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<400> SEQUENCE: 326

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> SEQ ID NO 327
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 327

gcgaaagatc gtataagtgg aactccatgg tacggtatgg acgtc 45

<210> SEQ ID NO 328
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 328

Ala Lys Asp Arg Ile Ser Gly Thr Pro Trp Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 329
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 329

gacatccaga tgacctcagtc tccatccctca ctgtctgcat ctgttaggaga cagagtacc	60
atcacttgctc gggcgagtca ggacattgcc gattattnag cctggtttca acagaaacca	120
gggaaaagccc ctaagtccct gatctttctc gcatccagtc tggaaaagtgc ggttccctta	180
aaggttcagcg gcagtggtatc tgggacagat ttcaactctca ccatcagcag cctgcagcct	240
gaagattttg caacttattta ctgccaacag tata>taggtt tcccgatcac cttcgccaa	300
gggaccaagg tggaaatcaa a	321

<210> SEQ ID NO 330
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 330

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ala Asp Tyr
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45

Phe Ala Ala Ser Ser Leu Glu Ser Trp Val Pro Leu Lys Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Arg Phe Pro Ile
85 90 95

-continued

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 331
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 331

caggacattg ccgattat

18

<210> SEQ ID NO 332
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 332

Gln Asp Ile Ala Asp Tyr
1 5

<210> SEQ ID NO 333
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 333

gctgcattcc

9

<210> SEQ ID NO 334
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 334

Ala Ala Ser
1

<210> SEQ ID NO 335
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 335

caacagtata gtaggttccc gatcacc

27

<210> SEQ ID NO 336
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 336

Gln Gln Tyr Ser Arg Phe Pro Ile Thr
1 5

-continued

<210> SEQ ID NO 337
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 337

caggtgcagc	tggtgaggc	tgggggaggc	gtggtccagc	ctgggaggc	cctgagactc	60
tcctgtgcag	cctctggatt	caccttcagt	aactatggca	tgcactgggt	ccgccaggct	120
ccaggcaagg	ggctggagt	ggtgacactc	atagaacatg	atggaagtaa	taaaaactat	180
gttagactccg	tgaagggccg	attcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
ctgcaaata	acagtctgag	agttgaggac	acggctgtat	attactgtgc	gaaagatcgt	300
ataactggaa	ctccatggta	cggtatggac	gtctgggccc	aagggaccac	ggtcaccgtc	360
tcctca						366

<210> SEQ ID NO 338
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 338

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
1				5			10				15				
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asn	Tyr
	20				25				30						
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35				40				45						
Thr	Leu	Ile	Glu	His	Asp	Gly	Ser	Asn	Lys	Asn	Tyr	Val	Asp	Ser	Val
	50				55				60						
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
	65				70				75			80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Val	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
	85				90				95						
Ala	Lys	Asp	Arg	Ile	Thr	Gly	Thr	Pro	Trp	Tyr	Gly	Met	Asp	Val	Trp
	100				105				110						
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser						
	115				120										

<210> SEQ ID NO 339
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 339

ggattcacct	tca	gtaacta	tggc	24
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<210> SEQ ID NO 340
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 340

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Gly Phe Thr Phe Ser Asn Tyr Gly
1 5

<210> SEQ ID NO 341
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 341

atagaacatg atggaagtaa taaa

24

<210> SEQ ID NO 342
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 342

Ile Glu His Asp Gly Ser Asn Lys
1 5

<210> SEQ ID NO 343
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 343

gcgaaagatc gtataactgg aactccatgg tacggtatgg acgtc

45

<210> SEQ ID NO 344
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 344

Ala Lys Asp Arg Ile Thr Gly Thr Pro Trp Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 345
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 345

gacatccaga tgacctcagtc tccatccctca ctgtctgcat ctgttaggaga cagagtacc

60

atcacttgtc gggcgagtca ggacattgcc gattatttag cctggtttca acagaaaacca

120

ggaaaaagccc ctaaatccct gatctttgcg gcatccagtc tggaaagtgc ggttccctta

180

aagttcagcg gcagtggtatc tggacagat ttcactctca ccatcagcag cctgcagcct

240

gaagattttg caacttatta ctgccaacag tataataggc tcccgatcac cttcggccaa

300

gggacacgac tggagattaa a

321

<210> SEQ ID NO 346
<211> LENGTH: 107

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 346

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1					5					10					15

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ala	Asp	Tyr
	20					25									30

Leu	Ala	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Ser	Leu	Ile
		35				40									45

Phe	Ala	Ala	Ser	Ser	Leu	Glu	Ser	Trp	Val	Pro	Leu	Lys	Phe	Ser	Gly
		50				55									60

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
		65			70				75						80

Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Arg	Phe	Pro	Ile
		85				90									95

Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys					
		100													105

<210> SEQ_ID NO 347

<211> LENGTH: 18

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 347

caggacattg ccgattat

18

<210> SEQ_ID NO 348

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 348

Gln Asp Ile Ala Asp Tyr
1 5

<210> SEQ_ID NO 349

<211> LENGTH: 9

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 349

gcggcatcc

9

<210> SEQ_ID NO 350

<211> LENGTH: 3

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 350

Ala Ala Ser
1

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<210> SEQ ID NO 351
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 351

caacagtata ataggttccc gatcacc

27

<210> SEQ ID NO 352
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 352

Gln Gln Tyr Asn Arg Phe Pro Ile Thr
1 5

<210> SEQ ID NO 353
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 353

gagggtgcagc	tgggtggagtc	tgggggaggc	ttgggtccagc	ctggggggtc	cctgaggctc	60
tcatgtgcag	cctctagatt	caccttttagt	acctattgga	tgagctgggt	ccgcccaggct	120
ccagggaaagg	ggctggagtg	ggtggccaaa	ataaagcaag	atggaagtga	gaaataactat	180
ctggactctg	tgaaggaccg	attcaccatc	tccagagaca	acgccaagaa	ctcactgtat	240
ctgcaaatga	acagcctgag	agccgaagac	acggctgtgt	attactgtgc	gagtagcatt	300
acctggtaacg	actactacta	cggtatggac	gtctggggcc	acgggaccac	ggtcacccgtc	360
tcctca						366

<210> SEQ ID NO 354
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 354

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Ser Thr Tyr
20 25 30Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45Ala Lys Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Leu Asp Ser Val
50 55 60Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95Ala Ser Ser Ile Thr Trp Tyr Asp Tyr Tyr Tyr Gly Met Asp Val Trp
100 105 110

-continued

Gly His Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 355
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 355

agattcacct ttagtaccta ttgg

24

<210> SEQ ID NO 356
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 356

Arg Phe Thr Phe Ser Thr Tyr Trp
1 5

<210> SEQ ID NO 357
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 357

ataaaagcaag atggaagtga gaaa

24

<210> SEQ ID NO 358
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 358

Ile Lys Gln Asp Gly Ser Glu Lys
1 5

<210> SEQ ID NO 359
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 359

gcgagtagca ttacctggta cgactactac tacggtatgg acgtc

45

<210> SEQ ID NO 360
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 360

Ala Ser Ser Ile Thr Trp Tyr Asp Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

-continued

<210> SEQ ID NO 361
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 361

```
gaaaatttgt tgacgcagtc tccagactt cagtctgtga ctccaaaaga gaaagtacc 60
atcacctgcc gggccagtca gagcattgg agtaacttac actggatcca gcagaaacca 120
gatcagtctc caaacctcct catcaagttt gttcccagt ctttcagg ggtccccctcg 180
aggttcagtg gcagtggtatc tgggacatg ttccacctca ccatcaatag cctggaaagct 240
gaagatgctg caacgttatta ctgtcatcag actaatttt tacctcacac tttcggcgga 300
gggaccaagg tggaaatcaa a 321
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<210> SEQ ID NO 362
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 362

```
Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
 1           5          10          15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Asn
 20          25          30

Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Asn Leu Ile
 35          40          45

Lys Phe Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
 50          55          60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
 65          70          75          80

Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Thr Asn Phe Leu Pro His
 85          90          95

Thr Phe Gly Gly Thr Lys Val Glu Ile Lys
 100         105
```

<210> SEQ ID NO 363
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 363

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cagagcattg gtagtaac 18
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<210> SEQ ID NO 364
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 364

```
Gln Ser Ile Gly Ser Asn
 1           5
```

<210> SEQ ID NO 365

US 9,132,192 B2

179**180**

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<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 365

tttgcttcc

9

<210> SEQ ID NO 366
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 366

Phe Ala Ser

1

<210> SEQ ID NO 367
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 367

catcagacta attttttacc tcacact

27

<210> SEQ ID NO 368
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 368

His Gln Thr Asn Phe Leu Pro His Thr
1 5

<210> SEQ ID NO 369
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 369

cagggtgcagc tgggtggagtc tgggggaggc gtgggtccagc ctggggaggc cctgagactc	60
tccctgtcgag cctctggatt caccttcagt atctatggca tgaactgggt ccgccagggt	120
ccaggcaagg ggctggactg ggtggcagtt atttcagatg atggaagtaa taaagactat	180
gttagactccg tgaggggtcg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatacga acagcctgag cgctgaagac acggctgtct attactgtgc gaaagatcgt	300
atcactggca ctcattacta cggttatggac gtctggggcc aagggaccac ggtcaccgtc	360
tcctca	366

<210> SEQ ID NO 370
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 370

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
1					5			10			15			

Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ile	Tyr
					20			25			30				

Gly	Met	Asn	Trp	Val	Arg	Gln	Gly	Pro	Gly	Lys	Gly	Leu	Asp	Trp	Val
					35			40		45					

Ala	Val	Ile	Ser	Asp	Asp	Gly	Ser	Asn	Lys	Asp	Tyr	Val	Asp	Ser	Val
					50			55		60					

Arg	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
					65			70		75		80			

Leu	Gln	Met	Asn	Ser	Leu	Ser	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85			90		95					

Ala	Lys	Asp	Arg	Ile	Thr	Gly	Thr	His	Tyr	Tyr	Gly	Met	Asp	Val	Trp
					100			105		110					

Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser						
					115			120							

<210> SEQ ID NO 371

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 371

ggattcacct tcagtatcta tggc

24

<210> SEQ ID NO 372

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 372

Gly	Phe	Thr	Phe	Ser	Ile	Tyr	Gly
1					5		

<210> SEQ ID NO 373

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 373

atttcagatg atggaagtaa taaa

24

<210> SEQ ID NO 374

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 374

Ile	Ser	Asp	Asp	Gly	Ser	Asn	Lys
1					5		

<210> SEQ ID NO 375

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<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 375

gcgaaagatc gtatcactgg cactcattac tacggatgg acgtc 45

<210> SEQ ID NO 376
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 376

Ala Lys Asp Arg Ile Thr Gly Thr His Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 377
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 377

gacatccaga tgacctcagtc	tccgtcctca ctgtctgcat	ctgtcgaga cagaatcacc	60
atcaattgtc gggcgagtca	ggacattgcc aattatttag	cctggtttca gcagaaacca	120
ggtaatgccc ctacgtccct	gatctatgct gcatccattt	tgcaaagtgg ggtccccatca	180
aaggttcagcg gcagtggtatc	tggcacatgt ttcactctca	ccatcaccag cctgcagcca	240
gaagattttg caagtttata	ctgccaacaa tataatagaa	agccgtggac gttcggccga	300
gggaccaagg tggaaatcaa	a		321

<210> SEQ ID NO 378
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 378

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15Asp Arg Ile Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ala Asn Tyr
20 25 30Leu Ala Trp Phe Gln Gln Lys Pro Gly Asn Ala Pro Thr Ser Leu Ile
35 40 45Tyr Ala Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
50 55 60Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Leu Gln Pro
65 70 75 80Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Tyr Asn Arg Lys Pro Trp
85 90 95Thr Phe Gly Arg Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 379
<211> LENGTH: 18

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 379

caggacattg ccaattat

18

<210> SEQ ID NO 380
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 380

Gln Asp Ile Ala Asn Tyr
1 5

<210> SEQ ID NO 381
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 381

gctgcattcc

9

<210> SEQ ID NO 382
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 382

Ala Ala Ser
1

<210> SEQ ID NO 383
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 383

caacaatata atagaaagcc gtggacg

27

<210> SEQ ID NO 384
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 384

Gln Gln Tyr Asn Arg Lys Pro Trp Thr
1 5

<210> SEQ ID NO 385
<211> LENGTH: 1210
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

-continued

Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala
 1 5 10 15
 Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln
 20 25 30
 Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe
 35 40 45
 Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn
 50 55 60
 Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys
 65 70 75 80
 Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val
 85 90 95
 Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr
 100 105 110
 Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn
 115 120 125
 Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu
 130 135 140
 His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu
 145 150 155 160
 Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met
 165 170 175
 Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro
 180 185 190
 Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Asn Cys Gln
 195 200 205
 Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg
 210 215 220
 Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys
 225 230 235 240
 Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp
 245 250 255
 Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro
 260 265 270
 Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly
 275 280 285
 Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His
 290 295 300
 Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu
 305 310 315 320
 Asp Gly Val Arg Lys Cys Lys Cys Glu Gly Pro Cys Arg Lys Val
 325 330 335
 Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn
 340 345 350
 Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp
 355 360 365
 Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr
 370 375 380
 Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val Lys Glu
 385 390 395 400
 Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp
 405 410 415

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Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln
 420 425 430
 His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu
 435 440 445
 Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser
 450 455 460
 Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu
 465 470 475 480
 Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu
 485 490 495
 Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro
 500 505 510
 Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn
 515 520 525
 Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu Gly
 530 535 540
 Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His Pro
 545 550 555 560
 Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro
 565 570 575
 Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val
 580 585 590
 Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp
 595 600 605
 Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys
 610 615 620
 Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly
 625 630 635 640
 Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu
 645 650 655
 Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His
 660 665 670
 Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu
 675 680 685
 Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu
 690 695 700
 Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser
 705 710 715 720
 Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu
 725 730 735
 Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser
 740 745 750
 Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser
 755 760 765
 Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser
 770 775 780
 Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp
 785 790 795 800
 Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn
 805 810 815
 Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg
 820 825 830
 Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro

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835	840	845
Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala		
850	855	860
Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp		
865	870	875
880		
Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp		
885	890	895
Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser		
900	905	910
Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu		
915	920	925
Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr		
930	935	940
Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys		
945	950	955
960		
Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln		
965	970	975
Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro		
980	985	990
Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp		
995	1000	1005
Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe Phe		
1010	1015	1020
Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu Ser Ala		
1025	1030	1035
1040		
Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn Gly Leu Gln		
1045	1050	1055
Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg Tyr Ser Ser Asp		
1060	1065	1070
Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp Asp Thr Phe Leu Pro		
1075	1080	1085
Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys Arg Pro Ala Gly Ser		
1090	1095	1100
Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu Asn Pro Ala Pro Ser		
1105	1110	1115
1120		
Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr Ala Val Gly Asn Pro		
1125	1130	1135
Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val Asn Ser Thr Phe Asp		
1140	1145	1150
Ser Pro Ala His Trp Ala Gln Lys Gly Ser His Gln Ile Ser Leu Asp		
1155	1160	1165
Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn		
1170	1175	1180
Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val		
1185	1190	1195
1200		
Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala		
1205	1210	

<210> SEQ ID NO 386

<211> LENGTH: 660

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic

-continued

<400> SEQUENCE: 386

Leu Glu Glu Lys Lys Val Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln
 1 5 10 15

Leu Gly Thr Phe Glu Asp His Phe Leu Ser Leu Gln Arg Met Phe Asn
 20 25 30

Asn Cys Glu Val Val Leu Gly Asn Leu Glu Ile Thr Tyr Val Gln Arg
 35 40 45

Asn Tyr Asp Leu Ser Phe Leu Lys Thr Ile Gln Glu Val Ala Gly Tyr
 50 55 60

Val Leu Ile Ala Leu Asn Thr Val Glu Arg Ile Pro Leu Glu Asn Leu
 65 70 75 80

Gln Ile Ile Arg Gly Asn Met Tyr Tyr Glu Asn Ser Tyr Ala Leu Ala
 85 90 95

Val Leu Ser Asn Tyr Asp Ala Asn Lys Thr Gly Leu Lys Glu Leu Pro
 100 105 110

Met Arg Asn Leu Gln Glu Ile Leu His Gly Ala Val Arg Phe Ser Asn
 115 120 125

Asn Pro Ala Leu Cys Asn Val Glu Ser Ile Gln Trp Arg Asp Ile Val
 130 135 140

Ser Ser Asp Phe Leu Ser Asn Met Ser Met Asp Phe Gln Asn His Leu
 145 150 155 160

Gly Ser Cys Gln Lys Cys Asp Pro Ser Cys Pro Asn Gly Ser Cys Trp
 165 170 175

Gly Ala Gly Glu Glu Asn Cys Gln Lys Leu Thr Lys Ile Ile Cys Ala
 180 185 190

Gln Gln Cys Ser Gly Arg Cys Arg Gly Lys Ser Pro Ser Asp Cys Cys
 195 200 205

His Asn Gln Cys Ala Ala Gly Cys Thr Gly Pro Arg Glu Ser Asp Cys
 210 215 220

Leu Val Cys Arg Lys Phe Arg Asp Glu Ala Thr Cys Lys Asp Thr Cys
 225 230 235 240

Pro Pro Leu Met Leu Tyr Asn Pro Thr Thr Tyr Gln Met Asp Val Asn
 245 250 255

Pro Glu Gly Lys Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro
 260 265 270

Arg Asn Tyr Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly
 275 280 285

Ala Asp Ser Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys
 290 295 300

Cys Glu Gly Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu
 305 310 315 320

Phe Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys
 325 330 335

Asn Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe
 340 345 350

Arg Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu
 355 360 365

Asp Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln
 370 375 380

Ala Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu
 385 390 395 400

Ile Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val
 405 410 415

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Val Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile
420 425 430

Ser Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala
435 440 445

Asn Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr
450 455 460

Lys Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln
465 470 475 480

Val Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro
485 490 495

Arg Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val
500 505 510

Asp Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn
515 520 525

Ser Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn
530 535 540

Ile Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His
545 550 555 560

Tyr Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met
565 570 575

Gly Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val
580 585 590

Cys His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly
595 600 605

Leu Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Cys
610 615 620

Pro Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gly Gly Glu
625 630 635 640

Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Gly His His His His His
645 650 655

His Ser Ser Gly
660

<210> SEQ ID NO 387
<211> LENGTH: 856
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

Leu Glu Glu Lys Val Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln
1 5 10 15

Leu Gly Thr Phe Glu Asp His Phe Leu Ser Leu Gln Arg Met Phe Asn
20 25 30

Asn Cys Glu Val Val Leu Gly Asn Leu Glu Ile Thr Tyr Val Gln Arg
35 40 45

Asn Tyr Asp Leu Ser Phe Leu Lys Thr Ile Gln Glu Val Ala Gly Tyr
50 55 60

Val Leu Ile Ala Leu Asn Thr Val Glu Arg Ile Pro Leu Glu Asn Leu
65 70 75 80

Gln Ile Ile Arg Gly Asn Met Tyr Tyr Glu Asn Ser Tyr Ala Leu Ala
85 90 95

Val Leu Ser Asn Tyr Asp Ala Asn Lys Thr Gly Leu Lys Glu Leu Pro
100 105 110

Met Arg Asn Leu Gln Glu Ile Leu His Gly Ala Val Arg Phe Ser Asn

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115	120	125
Asn Pro Ala Leu Cys Asn Val Glu Ser Ile Gln Trp Arg Asp Ile Val		
130	135	140
Ser Ser Asp Phe Leu Ser Asn Met Ser Met Asp Phe Gln Asn His Leu		
145	150	155
Gly Ser Cys Gln Lys Cys Asp Pro Ser Cys Pro Asn Gly Ser Cys Trp		
165	170	175
Gly Ala Gly Glu Glu Asn Cys Gln Lys Leu Thr Lys Ile Ile Cys Ala		
180	185	190
Gln Gln Cys Ser Gly Arg Cys Arg Gly Lys Ser Pro Ser Asp Cys Cys		
195	200	205
His Asn Gln Cys Ala Ala Gly Cys Thr Gly Pro Arg Glu Ser Asp Cys		
210	215	220
Leu Val Cys Arg Lys Phe Arg Asp Glu Ala Thr Cys Lys Asp Thr Cys		
225	230	235
Pro Pro Leu Met Leu Tyr Asn Pro Thr Thr Tyr Gln Met Asp Val Asn		
245	250	255
Pro Glu Gly Lys Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro		
260	265	270
Arg Asn Tyr Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly		
275	280	285
Ala Asp Ser Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys		
290	295	300
Cys Glu Gly Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu		
305	310	315
Phe Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys		
325	330	335
Asn Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe		
340	345	350
Arg Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu		
355	360	365
Asp Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln		
370	375	380
Ala Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu		
385	390	395
Ile Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val		
405	410	415
Val Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile		
420	425	430
Ser Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala		
435	440	445
Asn Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr		
450	455	460
Lys Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln		
465	470	475
480		
Val Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro		
485	490	495
Arg Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val		
500	505	510
Asp Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn		
515	520	525
Ser Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn		
530	535	540

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-continued

Ile Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His
 545 550 555 560

Tyr Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met
 565 570 575

Gly Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val
 580 585 590

Cys His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly
 595 600 605

Leu Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Glu
 610 615 620

Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala
 625 630 635 640

Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile
 645 650 655

Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val
 660 665 670

Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val
 675 680 685

Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp
 690 695 700

Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln
 705 710 715 720

Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp
 725 730 735

Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val
 740 745 750

Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Met Thr
 755 760 765

Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu
 770 775 780

Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr
 785 790 795 800

Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr
 805 810 815

Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr
 820 825 830

Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr Thr Lys
 835 840 845

Ser Phe Ser Arg Thr Pro Gly Lys
 850 855

<210> SEQ ID NO 388

<211> LENGTH: 227

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

-continued

50	55	60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr		
65	70	75
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly		
85	90	95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile		
100	105	110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val		
115	120	125
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser		
130	135	140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu		
145	150	155
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro		
165	170	175
Val Leu Asp Ser Asp Gly Ser Phe Leu Tyr Ser Lys Leu Thr Val		
180	185	190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met		
195	200	205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser		
210	215	220
Pro Gly Lys		
225		

What is claimed is:

1. An isolated antibody, or antigen-binding fragment thereof, that specifically binds human epidermal growth factor receptor (hEGFR), wherein the antibody or antigen-binding fragment comprises: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 130 and (b) the CDRs of a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 138.
2. The isolated antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment

comprises the heavy and light chain CDRs of a HCVR/LCVR amino acid sequence pair having SEQ ID NOS: 130/138.

3. The isolated antibody or antigen-binding fragment of claim 2, wherein the antibody or antigen-binding fragment comprises HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 domains, respectively, having SEQ ID NOS: 132-134-136-140-142-144.

4. A pharmaceutical composition comprising the antibody or antigen-binding fragment of claim 1, and a pharmaceutically acceptable carrier or diluent.

* * * * *